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PROTOCOL NUMBER: 800MS301/ NCT03870763

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, 3-Arm, Parallel-Group Study in Pediatric Subjects Aged 10 Through 17 Years to Evaluate the Efficacy and Safety of BG00012 and BIIB017 for the Treatment of Relapsing-Remitting Multiple Sclerosis

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SPONSOR SIGNATURE PAGE

Protocol 800MS301 was approved by:

[redacted], MD, PhD, MMSc

Biogen

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Date

(DD-Month-YYYY)

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1. SPONSOR INFORMATION

Biogen is responsible for initiating and managing the study.

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For urgent medical issues in which the study's Medical Monitor 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 (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

2. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
CI	confidence interval
CNS	central nervous system
CRF	case report form
CRO	contract research organization
DHA	Directions for Handling and Administration
DMF	dimethyl fumarate
DMT	disease-modifying therapy
DSMC	Data Safety Monitoring Committee
[redacted]	[redacted]
[redacted]	[redacted]
ELISA	enzyme-linked immunosorbent assay
FLS	flu-like symptoms
GA	glatiramer acetate
GCP	Good Clinical Practice
Gd	gadolinium
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IFN	interferon
[redacted]	[redacted]
[redacted]	[redacted]

ILM	Independent Laboratory Monitor
IM	intramuscular
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
IVMP	intravenous methylprednisolone
LAR	legally authorized representative
LLN	lower limit of normal
MMF	monomethyl fumarate
MRI	magnetic resonance imaging
MS	multiple sclerosis
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic
[redacted]	[redacted]
PEG	polyethylene glycol
PFS	prefilled syringe
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
[redacted]	[redacted]
RBC	red blood cell
RMS	relapsing multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SC	subcutaneous
[redacted]	[redacted]
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamate pyruvate transaminase
SUSAR	suspected unexpected serious adverse reaction
TID	3 times daily
TTFR	time to first relapse
ULN	upper limit of normal
WBC	white blood cell

3. SYNOPSIS

Protocol Number:	800MS301
Protocol Title:	A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, 3-Arm, Parallel-Group Study in Pediatric Subjects Aged 10 Through 17 Years to Evaluate the Efficacy and Safety of BG00012 and BIIB017 for the Treatment of Relapsing-Remitting Multiple Sclerosis
Version Number:	4
Name of Study Treatment:	BG00012 (dimethyl fumarate; Tecfidera®); BIIB017 (peginterferon beta-1a; Plegridy®)
Study Indication:	Relapsing-remitting multiple sclerosis (RRMS)
Study Rationale:	With limited availability of multiple sclerosis (MS) therapies for the pediatric population, there exists a significant need for safe, efficacious, and convenient treatment options. Given the pathophysiological similarities between adult and pediatric MS, therapies effective for MS in adults may also be effective in the pediatric population. BG00012 and BIIB017 are approved therapies for MS in adults. *BG00012* In adult subjects with RRMS, BG00012 has demonstrated a significant effect on clinical endpoints of relapse and disability, as well as on magnetic resonance imaging (MRI) endpoints of MS disease activity in 2 large Phase 3 studies (Study 109MS301 and Study 109MS302). The results from these 2 pivotal studies showed that BG00012 was well tolerated and has an acceptable safety profile. The extension study of these pivotal studies, Study 109MS303, confirmed the longer-term efficacy and safety of BG00012. Given the demonstrated efficacy and acceptable safety profile of BG00012 in adult subjects, together with the oral dosing regimen, BG00012 may be a potential treatment option for the pediatric population. *BIIB017* Interferon (IFN)-beta (β) therapies (Avonex®, Rebif®, Betaferon®, and Extavia®) have been shown to reduce relapse rates in adult subjects with RRMS with acceptable

safety and tolerability. The use of IFN-β in the pediatric MS population is well documented and appears to be well tolerated.

BIIB017, a polyethylene glycol (PEG) derivatized (PEGylated) form of IFN β-1a, has the same mechanism of action as non-PEGylated IFNs. A pivotal Phase 3 study (Study 105MS301) showed that BIIB017 was efficacious and safe in the adult RRMS population. The efficacy and safety of BIIB017 were confirmed in the extension study (Study 105MS302). While it is difficult to compare across studies, it appears that the efficacy and safety in adult RRMS population are similar between non-PEGylated and PEGylated IFNs. Given the previous experience of IFN use in the pediatric MS population and that BIIB017 has demonstrated similar safety profiles as non-PEGylated IFNs in the adult population, BIIB017 may be a potential treatment option for the pediatric population.

This 3-arm, parallel group study is being conducted in the pediatric population to evaluate the efficacy and safety of the following:

- BG00012 compared with placebo

and

- BIIB017 compared with placebo

Phase of Development: 3

Study Objectives and Endpoints:

The primary objective of the study is to evaluate the efficacy of BG00012 and BIIB017, both compared with placebo, in pediatric subjects with RRMS.

The primary endpoint that relates to this objective is the time to first relapse (TTFR).

The secondary objectives and endpoints are as follows:

- To evaluate the safety and tolerability of BG00012 and BIIB017
  - Occurrence of adverse events (AEs) and serious adverse events (SAEs)
- To assess the effect of BG00012 and BIIB017, both compared with placebo, on additional clinical and radiological measures of disease activity

- Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 48 and 96
- Number of gadolinium (Gd)-enhancing lesions at Baseline and at Weeks 48 and 96
- Annualized relapse rate at Weeks 48 and 96

Additional objectives and endpoints are listed in Section 6.3.

Study Design: This is a randomized, multicenter, double-blind, double-dummy, placebo-controlled, 3-arm, parallel-group study.

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

Number of Planned Subjects: Approximately 260 subjects will be enrolled.

Study Population: This study will be conducted in subjects aged 10 to 17 years, inclusive, with a diagnosis of RRMS as defined by the revised consensus definition for pediatric MS.

Detailed criteria are described in Section 8.

Treatment Groups: Subjects will be randomized in a 1:2:2 ratio to the following 3 treatment groups:

- Treatment Group 1: Approximately 52 subjects will receive BG00012 240 mg twice daily (BID) orally and placebo subcutaneous (SC) every 2 weeks for up to 96 weeks (2 years).
- Treatment Group 2: Approximately 104 subjects will receive BIIB017 125 µg SC every 2 weeks and placebo BID orally for up to 96 weeks (2 years).
- Treatment Group 3: Approximately 104 subjects will receive placebo SC every 2 weeks and placebo BID orally for up to 96 weeks (2 years)

Titration

Subjects randomized to BG00012 will receive a starting dose of 120 mg BID orally for 7 days followed by the maintenance dose of 240 mg BID for the remainder of the study.

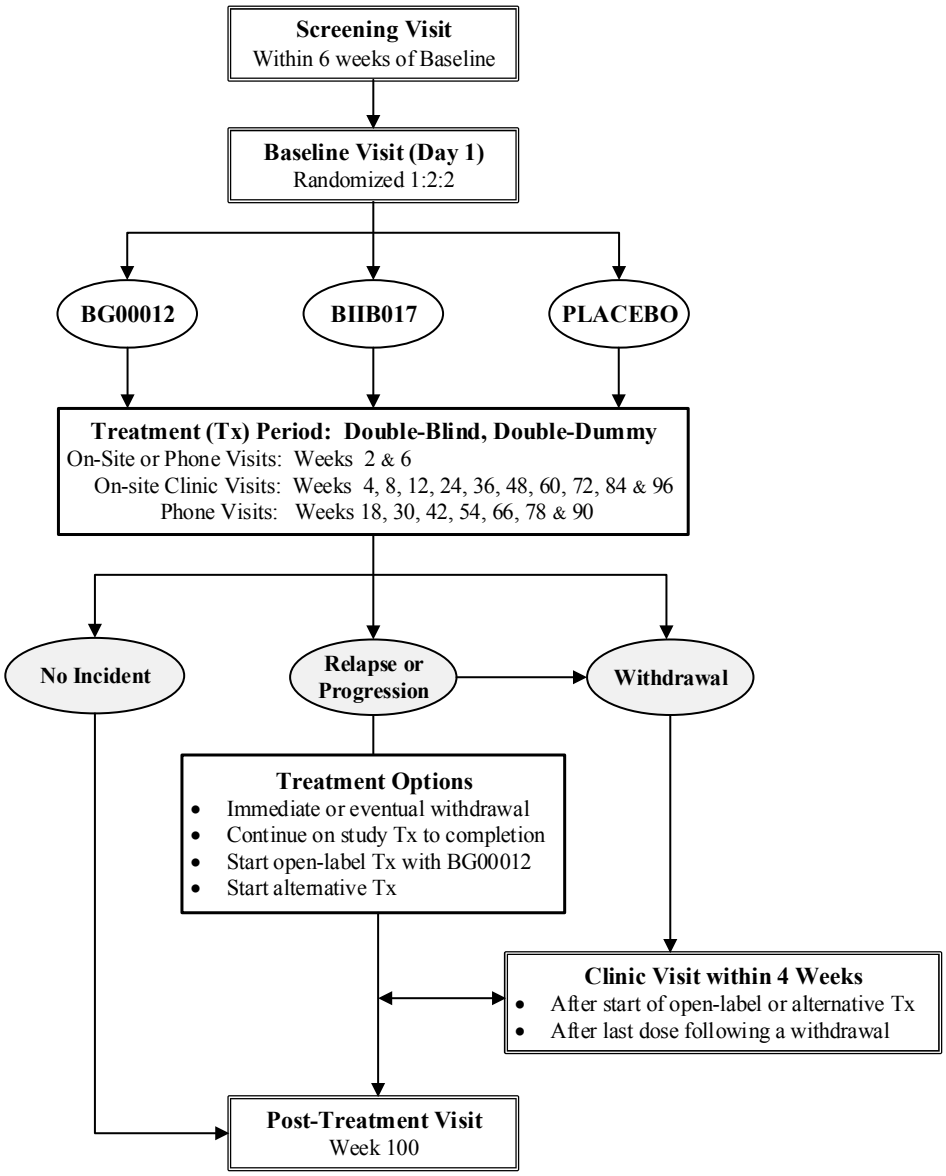
	Subjects randomized to BIIB017 will be titrated to the target dose of 125 µg SC: 63 µg on Day 1, 94 µg at Week 2, and 125 µg at Week 4. Once subjects reach the 125 µg target dose, they will continue on BIIB017 125 µg SC administered every 2 weeks for the remainder of the study.
Duration of Treatment and Follow-up:	Study duration for each subject will be approximately 106 weeks: a 6-week Screening Period, a 96-week (2-year) Treatment Period, and a 4-week Post-Treatment Period.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 800MS301

4.1. Study Schematic

The study design for Study 800MS301 is shown in Figure 1, and the study activities are shown in Table 1 and Table 2.

Figure 1: Study Design



4.2. Schedule of Activities

Table 1: Study Activities and Assessments

Tests and Assessments[1]	Screening Visit	Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Treatment Period														Post-Treatment Visit
Week	(Within 6 Weeks of Baseline)	Baseline Visit (Day 1)	Wk 2 ± 2 D (Option of clinic visit or 'phone call)	Wk 4 ±2 D	Wk 6 ± 2 D (Option of clinic visit or 'phone call)	Wk 8 ±7 D	Wk 12 ±7 D	Wk 24 ±7 D	Wk 36 ±7 D	Wk 48 ±7 D	Wk 60 ±7 D	Wk 72 ±7 D	Wk 84 ±7 D	Wk 96 ±7 D	'Phone Call (Wks 18, 30, 42, 54, 66, 78, 90 ± 7 D)	Wk 100 ±7 D
Informed Consent or Assent[2]	X															
Eligibility Criteria	X	X														
Randomization		X														
Medical History	X															
Physical Examination	X	X						X		X		X		X		X
Body Weight	X	X						X		X		X		X		X
Height[3]	X	X						X		X		X		X		
[redacted]																
HCV Ab, HBsAg Screen, HBsAb, HBcAb, PT, and aPTT	X															
HIV Testing[9]	X															
Serum Pregnancy Test[10]	X															
Urine Pregnancy Test[10,11]		X		X		X	X	X	X	X	X	X	X	X		X
[redacted]																

Tests and Assessments[1]	Screening Visit	Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Treatment Period														Post-Treatment Visit
Week	(Within 6 Weeks of Baseline)	Baseline Visit (Day 1)	Wk 2 ± 2 D (Option of clinic visit or 'phone call)	Wk 4 ±2 D	Wk 6 ± 2 D (Option of clinic visit or 'phone call)	Wk 8 ±7 D	Wk 12 ±7 D	Wk 24 ±7 D	Wk 36 ±7 D	Wk 48 ±7 D	Wk 60 ±7 D	Wk 72 ±7 D	Wk 84 ±7 D	Wk 96 ±7 D	'Phone Call (Wks 18, 30, 42, 54, 66, 78, 90 ± 7 D)	Wk 100 ±7 D
Brain MRI Scan ± Gd[13,14]		X								X				X		
Antibody Sampling[15]		X				X		X		X		X		X		
[redacted]																
Injection Training		X	Offered as necessary													
Dispense Study Treatment		X		X		X	X	X	X	X	X	X	X			
Administer/Monitor Injection at Clinic[17]		X	(X)	X	(X)											
Concomitant Therapy/ Procedures[18]			Monitor and record throughout the study													
SAE Recording			Monitor and record throughout the study													
AE Recording			Monitor and record throughout the study													

AE = adverse event; aPTT = activated partial thromboplastin time; D = days; [redacted]; Gd = gadolinium; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody ; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; [redacted]; PT = prothrombin time; [redacted]; SAE = serious adverse event; [redacted]; Wk = week.

[1] Tests and assessments must be completed prior to study treatment administration and/or distribution unless otherwise specified.
[2] 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.
[3] Height should be measured using stadiometry and recorded to the nearest 10th of a centimeter.
[redacted]

[redacted]

[8]Thyroid-stimulating hormone levels will be tested at Screening and every 12 weeks throughout the study.
[9] HIV testing will be performed at Screening, only if required by local regulations.
[10] For sexually active females of childbearing potential.
[11]All urine pregnancy testing will be performed at the site. Results must be known prior to dispensing study treatment.
[redacted]

[1] MRI must not be performed within 30 days of receiving a course of steroids.
[14]MRI must be performed within 14 days prior to first dose or on Day 1 (Baseline Visit) and at Week 48 ± 14 days, and at Week 96 ± 14 days.
[15] On the visits when subcutaneous injection is administered at the clinic, antibody samples are to be collected before dosing.
[redacted]

[17]Subjects are to self-administer (or parent is to administer) SC injection in the clinic from Baseline through Week 6.
[18]For the first 24 weeks of the study, all subjects will be instructed to take acetaminophen (paracetamol), ibuprofen, or other nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen prior to each injection and for the 24 hours following each injection at the recommended dose and frequency per the local labels. After the first 24 weeks of the study, acetaminophen, ibuprofen, or other NSAID treatment may be discontinued at the discretion of the Investigator.

Table 2: Study Activities and Assessments (Unscheduled Visits)

Tests and Assessment	Open-Label BG00012/Alternative Therapy Visit[2] (Within 4 Weeks after Switch if Next Study Visit not Within 4 Weeks)	Lymphocyte Follow-Up Visit(s)[3]	Relapse Evaluation Unscheduled Relapse Assessment Visit	Early Withdrawal Visit[1]
Telephone Questionnaire			X	
Relapse Assessment			X	
Physical Examination		X	X	X
Body Weight			X	X
Height[4]				X
[redacted]				
Urine Pregnancy Test[8]	X		X	X
[redacted]				
Antibody Sampling				X
[redacted]				
Brain MRI Scan ±Gd[10]			X	X
[redacted]				
Concomitant Therapy and Procedures, SAEs and AEs	X	X	X	X

AE = adverse event; [redacted]; SAE = serious adverse event; [redacted]; Wk = week.

[1]The Early Withdrawal Visit should be conducted no later than 4 weeks after the subject's last dose of study treatment or alternative therapy.

[2]The Open-Label BG00012/Alternative Therapy Visit includes assessments to be performed for subjects who either switch to open-label BG00012 or alternative therapy, or discontinue alternative therapy. Subjects will resume protocol visits and assessments as detailed in Table 1 while on BG00012/alternative therapy.

[3]Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN, or for 48 weeks following treatment discontinuation, whichever occurs sooner, or until the subject is initiated on the appropriate MS treatment, according to local standard of care, following study withdrawal/completion.

[4]Height should be measured using stadiometry and recorded to the nearest 10th of a centimeter.

[redacted]

[8]For sexually active females of childbearing potential. All urine pregnancy testing will be performed at the site. Results must be known prior to dispensing study treatment.

[redacted]

[10]A brain MRI scan will be performed unless assessed in the last 30 days. Except when conducted as part of relapse assessment, MRIs must not be performed within 30 days of receiving a course of steroids.

[redacted]

4.3. Additional Information

4.3.1. Administration of Study Treatment

To ensure blinding across the 3 treatment groups, each subject will receive BG00012 or placebo capsules administered orally BID and BIIB017 or placebo injection administered SC every 2 weeks. Subjects can either swallow the capsules whole (preferred) or open the capsules and mix with food **immediately** prior to consumption. If the subject is unable to self-administer the SC treatment, the parent will be allowed to administer the treatment.

4.3.2. Blood Volumes

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

Table 3: Blood Volumes by Visit

	Screening Visit	Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Treatment Period										Post-Treatment Visit
	(Within 6 Weeks of Baseline)	Baseline Visit (Day 1)	Wk 4 ±2 D	Wk 8 ±7 D	Wk 12 ±7 D	Wk 24 ±7 D	Wk 36 ±7 D	Wk 48 ±7 D	Wk 60 ±7 D	Wk 72 ±7 D	Wk 84 ±7 D	Wk 96 ±7 D	Wk 100 ±7 D
Blood draw volume (mL)	11.0	14.0	5.5	14.0	7.0	15.5	7.0	15.5	7.0	15.5	7.0	15.5	7.0

D = days; Wk = weeks

Table 4: Blood Volumes by Visit (Unscheduled Visits)

	Early Withdrawal Visit	Open-Label BG00012 (Tecfidera)/Alternative Therapy Visit (Within 4 Weeks after Switch if Next Study Visit not Within 4 Weeks)	Lymphocyte Follow-Up Visit	Unscheduled Relapse Assessment Visit
Blood draw volume (mL)	15.5	7.0	2.0	7.0

4.3.3. Site Personnel

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

- A primary and backup treating neurologist
- A primary and backup treating nurse or study coordinator
- A primary and backup examining neurologist
- A primary and backup examining technician
- A Magnetic Resonance Imaging (MRI) technician
- A pharmacist (or authorized designee)

The primary treating neurologist will be responsible for the following:

- Management of the routine neurological care of the subject
- Assessment (including assignment of causality) and treatment of AEs and MS relapses
- [redacted]
- Providing education to subjects on signs and symptoms of potential delayed reactions after injection, and signs and symptoms of a relapse, and providing information to the subject on how to contact the site to report any AE.

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

[redacted]

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

- Assisting the treating neurologist in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medications.
- [redacted]
- [redacted]
- Providing injection training as required.
- Collecting blood samples and obtaining vital signs.

[redacted]

The examining neurologist must not be involved with any other aspect of subject care and management and must remain blinded to AEs, concomitant medications, [redacted], MRI data, and any other data that have the potential of revealing the treatment assignment. Furthermore, the examining neurologist is not to serve as treating neurologist for any subjects at a given investigational site. To ensure consistency across sites, examining neurologists must undergo a standardized training session on [redacted] prior to enrollment of subjects at their site; this training session will be valid until the end of study. The backup examining neurologist will conduct a detailed neurological examination and obtain an [redacted] only if the primary examining neurologist is unavailable due to illness, vacation, or travel. All sites should attempt to maintain the same examining neurologist throughout the study. If an examining neurologist has to be replaced, the new examining neurologist must undergo a training session. The communication of new findings on the neurological examination from the examining neurologist to the treating neurologist is permitted (because findings on the neurological examination may be important in the routine care of the subject, e.g., medical management of relapses) and will be provided via source documentation. The roles of treating and examining neurologists (primary and backup) are not interchangeable even for different subjects. However, the examining neurologist may also act as the examining technician.

The examining technician (or the examining neurologist) will be responsible for administering the [redacted]

The examining technician must remain blinded to AEs, concomitant medications, [redacted], MRI data, and any other data that have the potential of revealing the treatment assignment. To ensure consistency across sites, examining technicians must undergo a standardized training session prior to enrollment of subjects at their site. All sites should attempt to maintain the same examining technician throughout the study. If an examining technician has to be replaced, the new examining technician must undergo a training session.

The MRI technician will be responsible for performing brain MRI scans with and without Gd at all protocol-required timepoints. Study-specific MRI scan procedures and protocols with and without Gd, which will be provided prior to study start, must be followed. Subjects should be offered the use of topical anesthetics for venipuncture, and an intravenous (IV) line insertion must be performed for injection of Gd.

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

5. INTRODUCTION

BG00012 is a fumarate ester drug product formulation containing the active ingredient dimethyl fumarate (DMF), which is rapidly and completely metabolized to monomethyl fumarate (MMF). BIIB017 is a PEGylated form of IFN β-1a.

BG00012 (as Tecfidera®) and BIIB017 (as Plegridy®) have been approved for the treatment of MS in adult populations in the United States, Canada, Australia, the European Union, and other countries.

5.1. Overview of Multiple Sclerosis

MS is a chronic and neurodegenerative disease of the central nervous system (CNS) that is characterized by inflammation, cell-mediated demyelination, and oligodendrocyte and neuronal loss. It is the most common demyelinating disorder of the CNS, affecting approximately 2.5 million people worldwide. The onset of MS typically occurs between the ages of 20 and 40 years [O'Connor and Group 2002]. Although rare in the pediatric population (patients less than 18 years of age), approximately 2% to 5% of all MS cases have onset in childhood [Atzori 2009; Chitnis 2009; Confavreux and Vukusic 2008; Ferreira 2008; Pohl 2007].

Pathologically, MS is characterized by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. Clinically, patients with MS exhibit a diverse range of neurological signs and symptoms attributed to white matter lesions that are disseminated in time and space; these signs and symptoms can occur in sudden attacks or can be insidious and progressive. The majority of patients with MS present with a RRMS course, during which patients experience discrete episodes of neurological dysfunction (i.e., relapses) that can last several days to several weeks, and that occur intermittently over many years [Lublin and Reingold 1996]. Disease progression and advancing disability supervene in the majority of patients who start with a relapsing remitting course (secondary progression). Disease progression can also begin insidiously from the onset of the disease (primary progression).

5.2. Current Therapies for Multiple Sclerosis

Therapies for MS include symptomatic treatments and disease-modifying therapies (DMTs). There are several DMTs that are currently approved or under review for use in patients with relapsing MS that differ in method of administration, convenience, efficacy, safety, and putative mechanism of action. They include IFN-β products (Avonex®, Rebif®, Betaseron®/Betaferon®/Extavia®, and Plegridy®), glatiramer acetate (GA; Copaxone®), natalizumab (Tysabri®), alemtuzumab (Lemtrada®), fingolimod (Gilenya™), mitoxantrone (Novantrone®), teriflunomide (Aubagio®), ocrelizumab (Ocrevus®) siponimod (Mayzent®), cladribine (Mavenclad®) and dimethyl fumarate (Tecfidera®).

The most commonly used therapies in the pediatric population are IFN-β and GA [Waldman 2011]. IFN-β and GA are first-line injectable therapies that have been available commercially

for more than 15 years and have an established safety and efficacy profile. The currently available IFN-β therapies and GA both require either intramuscular (IM) or SC injections, from as few as once every 2 weeks (PEGylated IFN β-1a SC) to once a week (IFN β-1a IM), to as many as 3 to 4 times a week (IFN β-1a SC, IFN β-1b SC) and 7 times a week (GA SC).

Despite the availability of several therapies for the treatment of MS in adults, there remains an unmet need for safe and effective treatments for the pediatric population. Currently, there are limited treatments that have been approved to treat MS in the pediatric population. Current treatment options for pediatric MS are frequently adapted from therapeutic paradigms for adults, with dosing recommendations based solely on adult data and expert opinion, because there are no available data on pharmacological characterization for any of these DMTs in the pediatric population.

5.3. Profile of Previous Experience With BG00012 and BIIB017

5.3.1. Nonclinical Experience With BG00012

Nonclinical safety studies were performed to support the development of BG00012 for the treatment of MS. CNS, respiratory, and cardiovascular safety studies demonstrated no drug-related adverse effects on those systems, which is consistent with human data. There were no findings of mutagenicity, fertility, and teratogenicity. Repeat-dose toxicology studies were performed in rodents (mouse and rat) and nonrodents (dog and monkey). The findings in the liver, forestomach, and testis were concluded to be of limited concern to human risk. In the male rat juvenile toxicology study that specifically evaluated the reproductive organs, there were no toxicology findings. Kidney findings seen in animals were not observed in humans. In 2-year (life-time) carcinogenicity studies, renal tumors were attributed to a rodent-specific nephropathy.

See the Investigator's Brochure for detailed information on nonclinical studies.

5.3.2. Clinical Experience With BG00012

The efficacy and safety of BG00012 are well established based on data from the clinical development program for BG00012 in adult subjects with MS. Over 4,700 subjects with MS have received BG00012 in the clinical trial setting, accounting for approximately 13,684 subject-years of exposure, as of 26 March 2019.

In 2 pivotal Phase 3 placebo-controlled studies, BG00012 demonstrated robust efficacy in subjects with RRMS (Studies 109MS301 and 109MS302). The results from these pivotal studies showed that 2 dosing regimens (240 mg BID and 240 mg 3 times daily [TID]) provided similar and consistent efficacy in reducing measures of relapse, delaying the accumulation of disability associated with MS, and resulted in improving MRI measures of MS disease activity. Treatment with BG00012 for up to 2 years resulted in statistically significant and substantial reductions in the risk of relapse and in annualized relapse rate in both studies. A robust treatment effect was evident within the initial 6 months of treatment and was sustained for up to 2 years of treatment.

Overall, safety data from the clinical development program showed that BG00012 was well tolerated and has an acceptable safety profile. The results from the 2 pivotal studies showed that both dosing regimens (240 mg BID and 240 mg TID) demonstrated similar and acceptable safety profiles in subjects with MS. The most common AEs (incidence ≥5%) that also occurred at an incidence of ≥2% higher in subjects treated with BG00012 compared with placebo 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.

In placebo-controlled studies, decreases in mean white blood cell (WBC) counts 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 (PML) has been observed in the setting of moderate to severe prolonged lymphopenia. With open-label and marketed use of BG00012, there has been no other evidence of increased risk of infections, serious infections, or opportunistic infections.

BG00012 was also associated with a small increase in the incidence of elevations of liver transaminases compared to placebo. In the controlled studies, this increase was primarily due to differences that occurred within the first 6 months of treatment. The majority of subjects with elevations had alanine transaminase (ALT) or aspartate transaminase (AST) levels <3 times the upper limit of normal (ULN). No patients had elevations of ALT or AST ≥3 × ULN associated with an elevation in total bilirubin of >2 × ULN. There were no cases of hepatic failure due to BG00012. During extended treatment with BG00012, ALT and AST levels remained stable through 3.5 years of observation. With marketed use of BG00012, liver function abnormalities (elevations in liver transaminases ≥3 × ULN with concomitant elevations in total bilirubin ≥2 × ULN) have been reported following BG00012 administration; these abnormalities resolved upon treatment discontinuation.

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, creatinine, electrolytes, calcium, phosphorus, parathyroid hormone, 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 on findings of 3+ or 4+ protein, both of which are potential indicators of significant proteinuria and renal dysfunction. In addition, there was no evidence of changes in β2-microglobulin and microalbumin, 2 more sensitive and specific markers of renal tubular dysfunction, over time, even during longer periods of observation of approximately 3.5 years.

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

5.3.3. Nonclinical Experience With BIIB017

The nonclinical toxicology testing of BIIB017 has shown that BIIB017 is well tolerated and has identified effects consistent with the known nonclinical experience with type I IFNs.

See the Investigator's Brochure for detailed information on nonclinical studies.

5.3.4. Clinical Experience With BIIB017

The Phase 3 multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study (Study 105MS301) evaluated the efficacy and safety of BIIB017 125 µg SC administered every 2 or 4 weeks in subjects with relapsing MS (RMS). In this study, 1512 subjects were dosed with either placebo or BIIB017.

The efficacy results from the placebo-controlled phase (Year 1) of Study 105MS301 demonstrate that BIIB017 produced meaningful reductions in clinical and radiological measures of MS disease activity. At Year 1, BIIB017 125 µg SC every 4 weeks and every 2 weeks had a statistically significant effect on the primary efficacy endpoint of annualized relapse rate and all secondary efficacy endpoints (proportion of subjects with relapse, number of new or newly enlarging T2 hyperintense lesions, and 12- and 24-week confirmed disability progression by EDSS) relative to placebo. The effect sizes were consistently larger for the BIIB017 every 2 weeks dose for all except for the risk of disability progression, which was similar for both doses. Efficacy was maintained through the second year of the study, especially in the BIIB017 every 2 weeks group. Statistically significant differences were observed in the BIIB017 125 µg SC every 2 weeks group compared with the BIIB017 125 µg SC every 4 weeks group for 2 years in relapse-related endpoints (reductions in annualized relapse rate and risk of relapse), the risk of 24-week confirmed disability progression, and the number of lesions on MRI (reductions in Gd-enhancing, new or newly enlarging T2 hyperintense, and new T1 hypointense lesions).

Safety data demonstrated that BIIB017 was generally well tolerated and had a very similar and favorable safety profile when administered as either an every 2- or 4-week dose. The safety profile of both BIIB017 treatment groups was consistent with the well-established safety profile of the IFN-β class of therapies currently approved for the treatment of patients with relapsing MS.

Most AEs that were reported in BIIB017-treated subjects were nonserious in nature and mild or moderate in severity. The most common adverse drug reactions (incidence ≥10%) in the BIIB017 every 2 weeks group were injection-site reactions (injection-site erythema, injection-site pain, and injection-site pruritus), flu-like symptoms (FLSs; influenza-like illness, pyrexia, myalgia, chills, asthenia, and arthralgia), and headache. Similar results were observed with the BIIB017 every 4 weeks group. Influenza-like illness, injection-site erythema, pyrexia, and ALT increased were the most frequently reported AEs leading to investigational product

discontinuation in BIIB017-treated subjects, and the incidence of each of these was ≤2% in each BIIB017 group. The incidence of SAEs was low and similar across treatment groups.

The incidence of hepatic disorders was low and consistent with the known hepatic AE profile of other IFN-β therapies. There was a dose-dependent increase in ALT and AST levels from baseline, but the majority of these elevations were <3 × ULN. Elevations of ALT and AST (>5 × ULN) were infrequently reported, and the incidence was balanced between the BIIB017 and placebo groups. Decreases in WBC counts (<3.0 × 10^9/L) were observed in a dose-related fashion in BIIB017-treated subjects and at a higher rate than in placebo-treated subjects. Mean WBC counts remained within normal limits throughout the study, and the decreases in WBC counts were not associated with an increased risk of infections or serious infections.

There was no increased risk of infection, serious infection, or opportunistic infection in the BIIB017-treated subjects as compared with placebo-treated subjects in Year 1 (the placebo-controlled phase) of Study 105MS301, and BIIB017 treatment did not increase the risk of cardiovascular disorders, seizure events, depression and suicidal ideation, autoimmune disorders, or malignancy. The safety results during the 2-year study period of Study 105MS301 were similar to those of Year 1 and demonstrated a similar safety profile for the BIIB017 every 4 weeks and every 2 weeks groups.

5.4. Study Rationale

With limited availability of MS therapies for the pediatric population, there exists a significant need for safe, efficacious, and convenient treatment options. Given the pathophysiological similarities between adult and pediatric MS [Chitnis 2013; Dale 2013; Hintzen and van Pelt 2013], therapies effective for MS in adults may also be effective in the pediatric population.

BG00012 and BIIB017 are approved therapies for MS in adults.

BG00012

In adult subjects with RRMS, BG00012 has demonstrated a significant effect on clinical endpoints of relapses and disability, as well as on MRI endpoints of MS disease activity in 2 large Phase 3 studies, Study 109MS301 and Study 109MS302. The results from these 2 pivotal studies showed that BG00012 was well tolerated and has an acceptable safety profile. The extension study of these pivotal studies, Study 109MS303, confirmed the longer-term efficacy and safety of BG00012. Given the demonstrated efficacy and favorable safety profile of BG00012 in adult subjects, together with the oral dosing regimen, BG00012 may be a potential treatment option for the pediatric population.

BIIB017

IFN-β therapies (Avonex, Rebif, Betaferon, and Extavia) are widely used injectable treatments and have been shown to reduce relapse rates in adults with RRMS. Avonex and Betaferon have shown to attenuate disease progression. Safety and tolerability of the IFN-β therapies have been well documented in several publications [Jacobs 2000; Johnson 1995; PRISMS Study Group 2001; The IFNB Multiple Sclerosis Study Group 1993]. The use of IFN-β in pediatric patients is well documented and appears to be well tolerated [Adams 1999; Banwell 2006; Ghezzi 2005;

Ghezzi 2009; Mikaeloff 2008; Mikaeloff 2001; Pohl 2005; Tenembaum and Segura 2006; Waubant 2001]. IFNs appear to be efficacious and safe in the pediatric population using the same doses as in the adult population.

Like other biologics, BIIB017, a polyethylene glycol (PEG; PEGylated) form of IFN β-1a, is believed to be absorbed through the lymphatic system and by blood capillary absorption after SC or IM administration. Given the molecular size of BIIB017 (~44 kDa), lymphatic absorption may dominate the bioavailability of BIIB017. The absorption, distribution, metabolism, and excretion of BIIB017 is expected to be mechanistically similar between the targeted pediatric subjects (10 to 17 years old) and adults.

BIIB017 has the same mechanism of action as non-PEGylated IFN-βs. Phase 1 study results showed that BIIB017 administered at 125 µg SC achieved pharmacological effects that were both consistent with activation of the Type 1 IFN receptor and similar to or greater than those observed after single doses of Avonex (IFN β-1a IM) 30 µg. A large pivotal Phase 3 study (Study 105MS301) showed that BIIB017 was efficacious and safe in the adult RRMS population. While it is difficult to compare across studies, it appears that the efficacy and safety in the adult RRMS population are similar between non-PEGylated IFN-β and PEGylated IFNs. Given the previous experience of IFN use in the pediatric MS population and that BIIB017 has demonstrated similar safety profiles as non-PEGylated IFNs in the adult population, BIIB017 may be a potential treatment option for the pediatric population.

This 3-arm, parallel-group study is being conducted in the pediatric population to evaluate the efficacy and safety of the following:

- BG00012 compared with placebo

and

- BIIB017 compared with placebo

5.5. Rationale for Dosing Regimen

BG00012 240 mg BID administered orally and BIIB017 125 µg administered SC every 2 weeks are the dosages chosen for this study.

BG00012

Biogen recently conducted Study 109MS202 (NCT02410200) to evaluate the pharmacokinetic/pharmacodynamic (PK/PD) of BG00012 in 22 subjects 10 to17 years of age with RRMS. Subjects received BG00012 120 mg BID for the first week and 240 mg BID for the remainder of the 24-week duration of treatment. The PK parameters in this study, as well as the neuroradiological efficacy and safety of BG00012, were consistent with those observed in adult MS patients. These findings indicate that 240 mg BID is the appropriate dosage for the current study.

BIIB017

The BIIB017 dose regimen was chosen based on the positive benefit-risk profile demonstrated in the Phase 3 study (105MS301). This dose is supported by a subgroup analysis, which

demonstrated that AE incidence in BIIB017-treated subjects was not sensitive to body mass index (BMI), a surrogate for exposure. This dose is further supported by results from modeling and simulation approaches. While there were marginal to modest increases in pediatric compared with adult median area under the concentration-time curve and maximum observed plasma concentration, the simulated PK profiles of pediatric subjects largely overlapped those of adult subjects due to high PK variability. Taken together, the findings indicate that 125 µg SC every 2 weeks is the appropriate dose for the current study.

5.5.1. Rationale for Comparator/Reference Product or Placebo

To date, there are few randomized, adequate, and well-controlled studies demonstrating that the agents available for treatment of MS in adults are safe and efficacious in pediatric patients. A placebo control, therefore, is appropriate to evaluate the safety and efficacy of new therapies. Utilizing an active control in this setting presents challenges in interpreting the results against a therapy that has not been previously evaluated rigorously in the target population, as well as challenges in logistic feasibility because such studies require a much larger sample size. To minimize any potential bias in the study conduct, a double-blind, double-dummy, 3-arm, parallel group, randomized design comparing BG00012 with placebo and BIIB017 with placebo was selected. Furthermore, with careful considerations regarding the potential ethical concerns of such design in pediatric patients, TTFR was selected as the primary efficacy endpoint for this study, as recommended by the International Pediatric Multiple Sclerosis Study Group (IPMSSG) [Krupp 2013] to allow study subjects to receive an alternative therapy (at the discretion of the treating neurologist) if they experience a protocol-defined relapse or disability progression.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy of BG00012 and BIIB017, both compared with placebo, in pediatric subjects with RRMS.

The primary endpoint that relates to this objective is the TTFR.

6.2. Secondary Objectives and Endpoints

The secondary objectives and endpoints are as follows:

- To evaluate the safety and tolerability of BG00012 and BIIB017
  - Occurrence of adverse events (AEs) and serious adverse events (SAEs)
- To assess the effect of BG00012 and BIIB017, both compared with placebo, on additional clinical and radiological measures of disease activity
  - Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 48 and 96
  - Number of Gd-enhancing lesions at Baseline and at Weeks 48 and 96
  - Annualized relapse rate at Weeks 48 and 96

[redacted]

[redacted]

7. STUDY DESIGN

7.1. Study Overview

This is a randomized, multicenter, double-blind, double-dummy, placebo-controlled, 3-arm, parallel-group study to evaluate the efficacy and safety of BG00012 and BIIB017 in pediatric subjects with RRMS.

Approximately 260 subjects, aged 10 to 17 years old, inclusive, with a diagnosis of RRMS as defined by the revised consensus definition for pediatric MS [Krupp 2013; Polman 2011] will be enrolled at approximately 50 sites globally. Eligible subjects will be randomized within 6 weeks of screening. At least 25% of subjects will be in the 10 to ≤14-year age group. Subjects will be stratified by age (10 to ≤14 years of age and 15 to 17 years of age) and by site. Subjects will be randomized (1:2:2) to treatment with BG00012, BIIB017, or placebo. Clinic visits will occur at Day 1 and at Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96. Clinic visits at Weeks 2 and 6 are optional and, if not conducted, will occur by 'phone. Subjects will be contacted by 'phone additionally at Weeks 18, 30, 42, 54, 66, 78, and 90. Subjects randomized to BG00012 will receive a starting dose of 120 mg twice daily (BID) orally for 7 days followed by the maintenance dose of 240 mg BID orally. Subjects randomized to BIIB017 will be titrated to the target dose of 125 µg: 63 µg on Day 1, 94 µg at Week 2, and 125 µg at Week 4. Once subjects reach the 125 µg target dose, they will continue on BIIB017 125 µg subcutaneous (SC) administered every 2 weeks for the remainder of the study. To ensure blinding across the 3 treatment groups, each subject will receive BG00012 or placebo administered orally BID and BIIB017 or placebo administered SC every 2 weeks.

An Unscheduled Relapse Assessment Visit may occur as required to conduct neurological and [redacted] evaluations within 72 hours of any new neurological symptoms that could indicate the onset of a clinical relapse. Confirmed relapses may be treated at the discretion of the treating neurologist with intravenous methylprednisolone (IVMP) at any time from Baseline to Week 100 and will not affect the subject's eligibility to continue in the study. The primary endpoint of the study is the TTFR. Therefore, subjects will be required to remain on assigned (blinded) study treatment until they experience their first protocol-defined relapse or disability progression.

During the study, subjects who have a confirmed relapse or disability progression or high lesion burden on MRI at Week 48 (defined as ≥9 new/enlarged T2 lesions) will have the option of switching to an alternative therapy in accordance with local practices, or open-label BG00012 (Tecfidera), at the discretion of the Investigator. Subjects will discontinue blinded study treatment when they switch to an alternative therapy or open-label BG00012. Subjects who are switched to an alternative therapy or open-label BG00012 will remain in the study to complete the scheduled visits, along with any requisite safety monitoring. Open-label BG00012 will only be provided until the subject completes or withdraws from the study or according to local regulatory requirements.

If a subject receives open-label BG00012 or an alternative therapy, they should be assessed at the Open-Label BG00012/Alternative Therapy Visit within 4 weeks of switching.

In addition to clinical monitoring for relapses, efficacy evaluations will include assessments of brain MRIs with Gd enhancement at Baseline and Weeks 48 and 96; [redacted] Safety will be evaluated by the occurrence of AEs and SAEs as well as [redacted]

Subjects who withdraw will complete the Early Withdrawal Visit no later than 4 weeks after the last dose of study treatment or alternative therapy.

Subjects whose lymphocyte count decreases to less than the lower limit of normal (LLN) while on study treatment will be followed at least every 4 weeks until the lymphocyte count is ≥LLN. Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN, or for 48 weeks following treatment discontinuation, whichever occurs sooner, or until the subject is initiated on the appropriate MS treatment, according to local standard of care, following study withdrawal/completion.

See Figure 1 for a schematic of the study design.

7.2. Study Specifics

7.2.1. Relapses

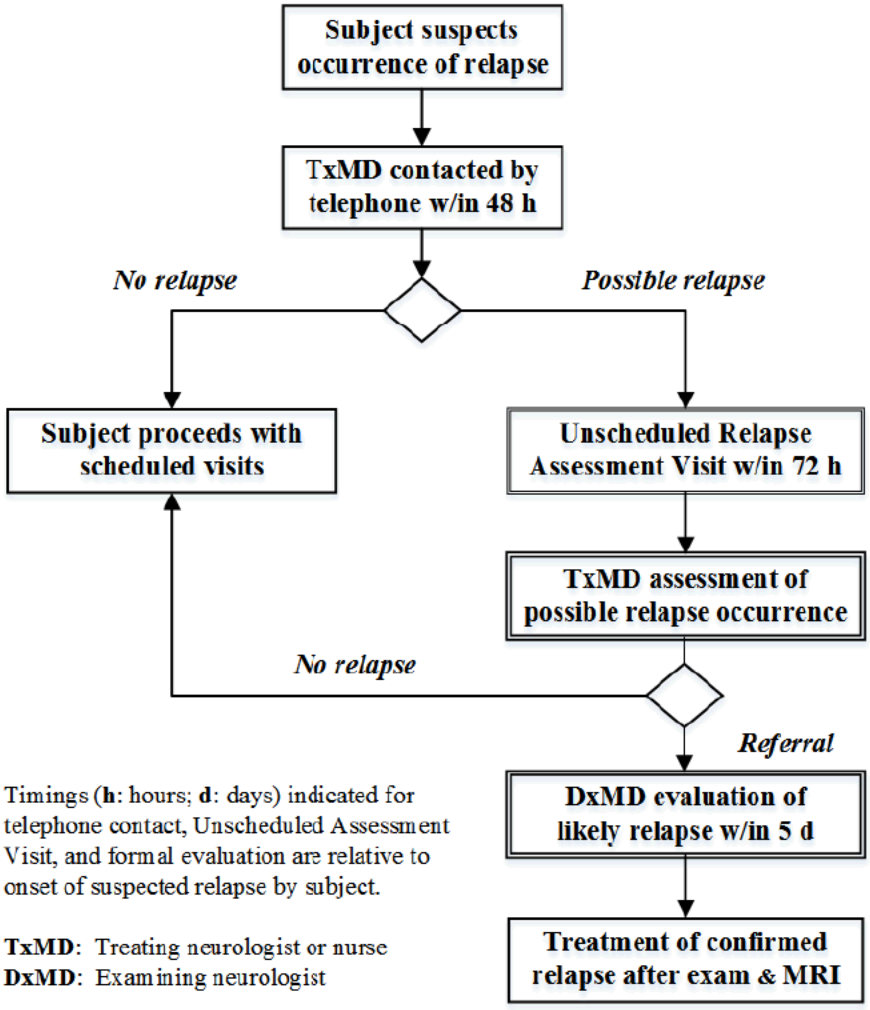
Relapses are defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. The examining neurologist must remain blinded to AEs, concomitant medications, laboratory data, MRI data, and any other data that have the potential of revealing the treatment assignment. The subject must have objective signs on the examining neurologist's examination confirming the event. New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse, and should not be treated with steroids. New or recurrent neurologic symptoms that occur less than 30 days following the onset of a protocol-defined relapse should be considered part of the same relapse and should not be treated with IVMP within protocol. Any changes to this treatment should first be discussed with the Medical Monitor. Steroid retreatment of the same relapse is not allowed unless approved by the Medical Monitor.

If a subject experiences new neurologic symptoms, the subject or parent must contact the treating nurse or treating neurologist as soon as possible within 48 hours of the onset of symptoms. A Telephone Questionnaire will be completed to determine the necessity of an Unscheduled Relapse Assessment Visit, wherein the subject will then be evaluated in person, if required, by the treating neurologist as soon as possible within 72 hours of the onset of the potential relapse. Additionally, all subjects must then be evaluated by the examining neurologist as soon as possible within 5 days of the onset of the symptoms. The examining neurologist will perform a

detailed neurological examination and obtain an [redacted]. These new objective findings on neurological examination by the examining neurologist are required to determine whether a suspected protocol-defined relapse has occurred. The examining neurologist's findings will be provided to the treating neurologist via source documentation so he/she can evaluate treatment options. Subjects may begin corticosteroid treatment of a confirmed relapse per protocol only after the examining neurologist has performed his/her examination and only after a Gd-enhancing MRI of the brain has been performed. See Figure 2 for a flow diagram of relapse evaluation.

If at any stage during relapse evaluation, i.e., the time of telephone contact, evaluation by the treating neurologist, and evaluation by the examining neurologist, the event is not determined to be a relapse, the specific reason for this determination must be recorded on the CRF.

Figure 2: Flow Diagram for Relapse Evaluation



Unscheduled relapse Assessment Visits are to be initiated within 72 hours of the onset of any new or worsening neurologic symptoms or suspected protocol-defined relapse. Unscheduled Relapse Assessment Visits should not modify or replace the subjects' visit schedule.

If a confirmed relapse occurs, the subject will be eligible to receive appropriate alternative therapy or open-label BG00012 at the discretion of the treating neurologist and will be allowed to remain in the study.

[redacted]

7.2.3. MS Relapses, Treatment, and Alternative MS Therapy

Subjects who suspect they are experiencing a relapse (new symptoms or worsening symptoms) are to telephone the treating Investigator within 48 hours of the onset of the symptoms (refer to Section 7.2.1 for further instructions regarding assessment of relapse).

Treatment of a confirmed acute event (relapse) with IVMP may proceed at any time from Baseline to Week 100 at the discretion of the treating Investigator only after the examining neurologist has completed his/her examination and a Gd-enhancing MRI of the brain has been performed; this will not affect the subject's eligibility to continue in the study. The treatment for relapse in this study is either 3 days or 5 days with IVMP, up to 1000 mg/day. Methylprednisolone can be given once a day or in divided doses. Any changes to this treatment should first be discussed with the Medical Monitor.

Subjects can continue on their assigned study treatment while being treated with IVMP.

During the study, subjects who have a confirmed relapse or disability progression or high lesion burden on MRI at Week 48 (defined as ≥9 new/enlarged T2 lesions) will have the option of switching to an alternative therapy in accordance with local practices, or open-label BG00012, at the discretion of the Investigator. Subjects will discontinue blinded study treatment when they switch to an alternative therapy or open-label BG00012. Subjects who are switched to an alternative therapy or open-label BG00012 will remain in the study to complete the scheduled visits, along with any requisite safety monitoring. Open-label BG00012 will only be provided until the subject completes or withdraws from the study or according to local regulatory requirements.

Subjects may choose to stop study treatment or permanently withdraw from the study at any time for any reason. Subjects who choose to stop study treatment at any time for any reason may choose to remain in the study for scheduled visits.

7.2.4. Study Treatment Holding and/or Stopping Rules

Study treatment administration can be held or stopped for clinical or laboratory abnormalities deemed clinically significant by the Investigator and/or abnormal laboratory values as defined in Table 5.

7.3. Overall Study Duration and Follow-Up

The study period will consist of Screening (up to 6 weeks), Treatment Period (up to 96 weeks), and Post-Treatment Period (4 weeks after the last dose of study treatment or alternative therapy).

Subjects who are allowed to resume study treatment following an interruption will restart dosing at a reduced dose and will be titrated to the maintenance dose.

Subjects who withdraw prematurely will complete the Early Withdrawal Visit no later than 4 weeks after taking their final dose of study treatment or alternative therapy. Unscheduled Relapse Assessment Visit and Lymphocyte Follow-Up Visit will be performed as necessary.

7.3.1. Screening

Subject eligibility for the study will be determined within 6 weeks prior to study entry. The Screening Period begins on the day the subject signs the informed consent form (ICF).

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment at Baseline (Day 1) and at Weeks 4, 8, 12, 24, 36, 48, 60, 72, and 84. Clinic visits at Weeks 2 and 6 are optional and, if not conducted, will occur by 'phone. Subjects will receive treatment for 96 weeks. Subjects who switch to open-label BG00012 or an alternative therapy and who are assessed at an Open-Label BG00012/Alternative Therapy Visit will then follow the same schedule for assessments as subjects remaining on their original study treatment.

7.3.3. Follow-Up

Subjects are to return to the study site for a follow-up visit at Week 100. The final study visit will be at Week 100 or 4 weeks after the last dose of study treatment or alternative therapy.

Subjects who withdraw prematurely from the study will complete the Early Withdrawal Visit no later than 4 weeks after taking their last dose of blinded study treatment, open-label BG00012 or alternative therapy. Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is ≥LLN, or for 48 weeks following treatment discontinuation, whichever occurs sooner, or until the subject is initiated on the appropriate MS treatment, according to local standard of care, following study withdrawal/completion.

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 the time of randomization (Day 1) or at the timepoint specified in the individual eligibility criterion listed:

1. Ability of a legally authorized representative (LAR; parent or legal guardian) 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 LAR's consent, as appropriate, per local regulations.

2. Aged 10 to 17 years old, inclusive, at the time of informed consent. The minimum age can be older than 10 years as required by country-specific regulations and/or local ethics committees.

3. Must have a diagnosis of RRMS as defined by the revised consensus definition for pediatric MS [Krupp 2013; Polman 2011].

4. Must have an EDSS score between 0.0 and 5.0.

5. Must have a body weight of ≥30 kg; the minimum weight for inclusion in the study may be greater than 30 kg if required by country-specific regulations and/or local ethics committees.

6. Must have experienced ≥1 relapse in the 12 months prior to randomization (Day 1), or must have evidence of asymptomatic disease activity (Gd-positive lesions) seen on MRI in the 6 months prior to randomization (Day 1), or must have ≥2 relapses in the 24 months prior to randomization (Day 1). Relapse is defined as the occurrence of a clinical demyelination event regardless of whether the event is a first (initial) or subsequent (recurrent) demyelinating event.

7. Sexually active subjects of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 3 months 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 the time of randomization (Day 1) or at the timepoint specified in the individual criterion listed:

Medical history

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

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

3. History of severe allergic or anaphylactic reactions or known drug hypersensitivity.

4. Known allergy to any component of DMF, fumaric acid esters, or BIIB017 formulation.

5. History of clinically significant cardiovascular, pulmonary, GI, hepatic, renal, endocrinologic, hematologic, immunologic, metabolic, dermatologic, growth, developmental, psychiatric (including depression), neurologic (other than MS), and/or other major disease and/or laboratory abnormality indicative thereof, that would preclude participation in a clinical study.

6. History of malignant disease, including solid tumors and hematologic malignancies, with the exception of basal cell and squamous cell carcinomas of the skin that have been completely excised and are considered cured.

7. History of seizure disorder or unexplained blackouts or history of a seizure within 3 months prior to randomization (Day 1).

8. History of suicidal ideation within 3 months prior to randomization (Day 1) or an episode of severe depression within 3 months prior to randomization (Day 1). Severe depression is defined as an episode of depression that requires hospitalization or is otherwise regarded as severe by the Investigator.

9. Clinically significant abnormal ECG values as determined by the Investigator.

10. History of human immunodeficiency virus (HIV) infection. Note: HIV testing will be performed at Screening, only if required by local regulations.

11. Known history or positive test result for hepatitis C antibody, or current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or positive for hepatitis B core antibody [HBcAb]) at Screening. Subjects with immunity to hepatitis B from either active vaccination (defined as negative HBsAg, positive hepatitis B surface antibody [HBsAb], and negative HBcAb) or from previous natural infection (defined as negative HBsAg, positive HBsAb immunoglobulin G, and positive HBcAb) are eligible to participate in the study (definitions are based on the Centers for Disease Control and Prevention [CDC] interpretation of the hepatitis B serology panel [CDC 2007]).

12. Abnormal screening blood tests exceeding any of the following limits defined below:

    - alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT) >2 × upper limit of normal (ULN), aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase (SGOT) >2 × ULN, gamma glutamyl transferase >2 × ULN, or bilirubin >1.5 × ULN
    - total WBC count <3700/mm^3
    - absolute neutrophil count (ANC) of <1500/mm^3
    - platelet count <150,000/mm^3
    - absolute lymphocyte count ≤ LLN
    - eosinophils >0.7× 10^3/μL or >0.7 GI/L
    - hemoglobin <10 g/dL in female subjects or <11 g/dL in male subjects
    - serum creatinine >ULN
    - prothrombin time or activated partial thromboplastin time >1.2 × ULN

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

OR

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

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

14. Occurrence of an MS relapse within the 30 days prior to randomization (Day 1) and/or the subject has not stabilized from a previous relapse prior to randomization.

Treatment history

15. Any previous treatment with Fumaderm®, BG00012, or BIIB017.

16. History of hypersensitivity or intolerance to acetaminophen (paracetamol), ibuprofen, or naproxen that would preclude use of at least 1 of these during the study.

17. Treatment with other agents to treat MS symptoms or underlying disease as specified below:

    - Prior treatment with any of the following:
        - total lymphoid radiation
        - cladribine
        - T-cell or T-cell receptor vaccine
        - any therapeutic monoclonal antibody (e.g., rituximab, natalizumab, or alemtuzumab)
    - Prior treatment with any of the following within 12 months prior to randomization (Day 1):
        - cyclophosphamide
        - mitoxantrone
    - Prior treatment with any of the following within 6 months prior to randomization (Day 1):
        - cyclosporine
        - fingolimod
        - plasma exchange or cytapheresis
        - IV immunoglobin
        - azathioprine
        - mycophenolate mofetil
        - methotrexate
        - teriflunomide
        - laquinimod
    - Prior treatment with systemic corticosteroids, including agents that may act through the corticosteroid pathway (e.g., low-dose naltrexone) within 30 days prior to randomization (Day 1).

- Prior treatment with GA, IFN, or 4-aminopyridine or related products (except subjects on a stable dose of controlled-release fampridine for at least 3 months) within 4 weeks prior to randomization (Day 1).

- Prior treatment that might influence growth, including but not limited to methylphenidate hydrochloride, thyroid hormone, growth hormone, anabolic steroids, calcitonin, estrogens, progestins (with the exception of medication used for contraception), bisphosphonates, anticonvulsants, or phosphate-binding antacids.

18. Treatment with another investigational drug or approved therapy for investigational use within the 6 months prior to randomization (Day 1).

Miscellaneous

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

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

21. Subjects for whom MRI is contraindicated (e.g., who have pacemakers, other contraindicated implanted metal devices, or embedded metals such as dental braces, tattoos, body piercings, etc.), or who are allergic to Gd, or have claustrophobia that cannot be medically managed.

22. Current enrollment in any other investigational drug study.

23. Previous randomization in this study.

24. Elective surgery performed within 2 weeks prior to randomization (Day 1).

25. Unwillingness or inability to comply with the study requirements.

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

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

The subject's LAR (e.g., parent or legal guardian, where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). When the ICF is signed, 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. Randomization and Registration of Subjects

Subjects will be registered and randomized at Baseline (Day 1), after all baseline and screening 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) and randomization. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

Subjects will be randomized in a 1:2:2 ratio to receive BG00012:BIIB017:placebo. Subjects will be stratified by age (10 to ≤14 years of age and 15 to 17 years of age) and by site.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This is a randomized, double-blind, double-dummy, placebo-controlled study.

All study staff will be blinded to the subject treatment assignments. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or at Biogen.

To ensure blinding across the 3 treatment groups, each subject will receive BG00012 or matching placebo administered orally BID and BIIB017 or matching placebo administered SC every 2 weeks. Subjects must NOT take a dose of BG00012 or matching placebo within the 4 hours prior to their scheduled appointment. This should prevent any drug-induced symptoms from being observed by study personnel during the evaluation and prevent possible unblinding of study personnel. When the subject has finished all evaluations and has left the clinic, the subject is to resume their dosing schedule. Whenever possible, study personnel (e.g., the treating nurse) should contact the subject the day before the scheduled appointment to remind the subject of these dosing restrictions. Additionally, to reduce the likelihood that injection site reactions and FLS associated with BIIB017 could unblind subjects and/or study personnel, all subjects will be instructed to take acetaminophen, ibuprofen, or nonsteroidal anti-inflammatory drugs (NSAIDs)

such as naproxen prior to each injection and for the 24 hours following each injection, for the first 24 weeks of the study. After the first 24 weeks of the study, acetaminophen, ibuprofen, or other NSAID treatment may be discontinued at the discretion of the Investigator.

White blood cell count (WBC) and differentials (including ANC and lymphocyte count) data that are obtained after the Screening Visit will not be sent to the sites and should not be reviewed by any site personnel, since these data can potentially compromise the blind of the study. The WBC and differentials data will be reviewed by an Independent Laboratory Monitor (ILM). Only laboratory abnormalities in WBC and differentials that meet the threshold limits in Table 5, as determined by the ILM, will be communicated to the sites.

At the end of the study (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, Biogen will provide the randomization codes to Investigators, who then can inform subjects about the treatment received.

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

10.1. Discontinuation of Study Treatment

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

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject experiences severe depression or suicidal ideation. Severe depression is defined as an episode of depression that requires hospitalization or is otherwise regarded as severe by the Investigator.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject experiences a medical emergency that necessitates unblinding of the subject's treatment assignment.
- The subject is unable to tolerate study treatment.
- At the discretion of the Investigator, the subject discontinues study treatment due to medical reasons or for noncompliance.
- The subject experiences a protocol-specified change in laboratory values that necessitates permanent discontinuation of treatment (Table 5).
- The subject develops lymphocyte count <500/mm^3 for more than 6 months (Table 6).
- The subject experiences more than 1 deviation of the same laboratory parameter that meets the threshold limits defined in Table 5 at any time during the study.
- The subject experiences more than 2 deviations of different laboratory parameters that meet the threshold limits defined in Table 5 at any time during the study.
- The subject develops renal dysfunction based on a nephrologist's evaluation.
- The subject is diagnosed with PML.

In the event of a subject experiencing a seizure or suspected seizure during the study, they should be managed as per local clinical guidelines/standard medical care. The Investigator should re-evaluate whether the subject should continue in the study.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

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

If a subject switches to an alternative therapy, the study treatment must be permanently discontinued, and the subject cannot go back on that study treatment.

10.2. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- 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 CRF.

Subjects who withdraw prematurely will complete the Early Withdrawal Visit no later than 4 weeks after taking their last dose of study treatment or alternative therapy.

11. STUDY TREATMENT USE

11.1. Regimen

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

Subjects are to contact the Investigator immediately if more than the prescribed dose is taken. If a dose is missed, the dose should be taken as soon as possible. If it is almost time for the next dose, the subject should skip the missed dose and go back to their regular dosing schedule. Doses should not be doubled to make up for missed doses.

11.1.1. BG00012

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

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

11.1.2. BIIB017

BIIB017 will be taken at a dose of 125 µg SC every 2 weeks for 96 weeks (2 years).

To mitigate FLS, all subjects randomized to receive BIIB017 treatment will be titrated to the target dose of 125 µg: 63 µg BIIB017 on Day 1, 94 µg at Week 2, and 125 µg at Week 4. Once subjects reach the 125 µg target dose, they will continue on this dose for the remainder of the study.

11.1.3. Placebo

Subjects will receive placebo using a regimen matching that for the BG00012 and BIIB017 treatment groups, during the maintenance as well as titration periods.

To ensure blinding across the 3 treatment groups, each subject will receive BG00012 or matching placebo administered orally BID and BIIB017 or matching placebo administered SC every 2 weeks.

11.2. Modification of Dose and/or Treatment Schedule

11.2.1. Dose Reduction

Dose reduction will be allowed only for subjects who are unable to tolerate BG00012 *due to flushing and/or GI disturbances* (dose reductions will not be allowed for abnormal laboratory values). Subjects who do not tolerate BG00012 will reduce their dose by taking one 120 mg capsule BID for up to 4 weeks. Within 4 weeks at the reduced dose, subjects will resume taking 2 capsules BID. If the subject is still unable to tolerate BG00012, the subject must discontinue BG00012 as described in Section 10.1. Any subject who prematurely discontinues dosing with BG00012 may remain in the study and continue protocol-scheduled tests and assessments.

11.2.2. Dosing Interruption for Abnormal Laboratory Values

Blinded study treatment or alternative therapy with BG00012 or BIIB017 must be temporarily or permanently withheld when any of the following laboratory values meet the threshold limits defined in Table 5. Laboratory abnormalities in WBC and differentials (including ANC and lymphocyte count) that meet the threshold limits in Table 5, as determined by the ILM, will be communicated to the sites.

Table 5: Laboratory Criteria Requiring Withholding or Permanent Discontinuation of Study Treatment or Alternative Therapy with BG00012 or BIIB017

Laboratory Parameter	Laboratory Result	Required Action
WBC	$<2000/mm^3$	The Investigator[1] should repeat the test as soon as possible. If retest value confirms WBC count $<2000/mm^3$ study treatment should be withheld and the test repeated approximately every 2 weeks. If the value remains $<2000/mm^3$ $\geq$4 weeks after discontinuation of study treatment, the subject **must *permanently* discontinue study treatment and the event must be recorded as an AE.**
	$<500/mm^3$	The Investigator[1] should repeat the test as soon as possible, and if the retest confirms WBC $<500/mm^3$, the Investigator will be informed of the laboratory value immediately. Study treatment should be withheld and retesting will be performed as documented in the required action for WBC $<2000/mm^3$. **Medical evaluation should be conducted as appropriate and the event must be recorded as an AE.**
ANC	$<750/mm^3$	The Investigator[1] should repeat the test as soon as possible. If the retest value confirms ANC $<750/mm^3$, the study treatment should be withheld, and the test repeated approximately every 2 weeks. If the value remains $<750/mm^3$ $\geq$4 weeks after discontinuation of study treatment, the subject **must *permanently* discontinue study treatment and the event must be recorded as an AE.**
	$<100/mm^3$	The Investigator[1] should repeat the test as soon as possible, and if the retest value confirms ANC $<100/mm^3$, the Investigator will be informed of the laboratory value immediately. Study treatment should be withheld and retesting will be performed as

Laboratory Parameter	Laboratory Result	Required Action
		documented in the required action for ANC <750/mm³. **Medical evaluation should be conducted as appropriate and the event must be recorded as an AE**.
Platelets	<75,000/mm^3	The Investigator[1] should repeat the test as soon as possible. If the retest value confirms platelets <75,000/mm³, study treatment should be withheld and the test repeated approximately every 2 weeks. If the value remains <75,000/mm^3 ≥4 weeks after discontinuation of study treatment, the **subject must *permanently* discontinue study treatment and the event must be recorded as an AE.**
	<25,000/mm^3	The Investigator[1] should repeat the test as soon as possible, and if the retest value confirms platelets <25,000/mm³, study treatment should be withheld and retesting will be performed as documented in the required action for platelets <75,000/mm³. **Medical evaluation should be conducted as appropriate and the event must be recorded as an AE.**
Hemoglobin	<8.5 g/dL	The Investigator[1] should repeat the test as soon as possible. If the retest value confirms hemoglobin <8.5 g/dL, study treatment should be withheld and the test repeated approximately every 2 weeks. If the value remains <8.5 g/dL ≥4 weeks after discontinuation of study treatment, the **subject must *permanently* discontinue study treatment and the event must be recorded as an AE.**
	<8.0 g/dL	The Investigator[1] should repeat the test as soon as possible, and if the retest value confirms hemoglobin <8.0 g/dL, study treatment should be withheld and retesting will be performed as documented in the required action for hemoglobin <8.5 g/dL. **Medical evaluation should be conducted as appropriate and the event must be recorded as an AE.**
AST (SGOT) or ALT (SGPT)	>3 × ULN	The Investigator[1] should repeat the test as soon as possible. If the retest value confirms ALT or AST > 3× ULN, study treatment should be withheld, and liver tests (ALT, AST, alkaline phosphatase, and total bilirubin) should be retested within 1 to 2 weeks. If, on retesting, the ALT or AST remains >3 × ULN, the **subject must *permanently* discontinue study treatment and the event must be recorded as an AE.**
ALT or AST and total bilirubin	ALT or AST ≥3× ULN and total bilirubin >2 × ULN in combination	The Investigator[1] should repeat the test as soon as possible. If the retest value confirms ALT or AST ≥3 × ULN and total bilirubin >2 × ULN in combination, 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, the study treatment should be withheld and the test repeated approximately every 2 weeks. 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
Urinalysis	Positive hematuria on microscopy	The Investigator should repeat the test as soon as possible. If retest confirms microscopic hematuria without known etiology, the study treatment should be withheld and the test repeated approximately every 2 weeks, and urine cytology must be performed. (**Note**: Urine cytology should be performed only once per episode of hematuria and does not have to be repeated). If hematuria persists for ≥4 weeks after discontinuation of study treatment or if cytology is positive, 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; ANC = absolute neutrophil count; AST = aspartate transaminase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal; WBC = white blood cell.

[1]WBC (including the differential) obtained after the Screening visit will not be sent to the sites and will not be reviewed by any site personnel, as these data could potentially compromise the blinding of the study. All other laboratory data will be reviewed by the sites. An Independent Laboratory Monitor (ILM) will regularly assess masked WBC counts and differentials (including ANC and lymphocyte count) in order to monitor subject safety, and may contact the sites to request additional information on an individual subject to confirm the safety of the subject or may request repeat blood testing. The ILM will apply the above prespecified laboratory criteria pertaining to WBC, ANC, and lymphocyte count that will result in withholding or permanent discontinuation of study treatment, and will communicate these instructions to the sites. In the setting of a medical emergency, as always, Investigators may perform local testing if needed for the care of the subject.

While dosing is withheld, subjects will continue tests and assessments according to the schedule defined in the protocol (and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice). In addition, subjects (whether dosing temporarily withheld or permanently discontinued) must have the abnormal laboratory result rechecked approximately every 2 weeks unless otherwise specified in the protocol, until resolution or stabilization of the laboratory value (rechecks will be run at the central laboratory). Depending on the severity and clinical significance of the abnormality, the Investigator may need to perform the retests more frequently.

Subjects who have abnormal laboratory values as described in Table 5 that are sustained for more than 4 consecutive weeks must permanently discontinue dosing with study treatment or alternative therapy.

11.2.3. Resumption of Study Treatment Dosing

Resumption of study treatment or alternative therapy is to be considered on a case-by-case basis and must be discussed with the Medical Monitor. However, subjects who have abnormal laboratory values, as described in Table 5, that are sustained for more than 4 consecutive weeks must permanently discontinue dosing with study treatment or alternative therapy.

Subjects with abnormal laboratory values, who are allowed to resume study treatment or alternative therapy dosing following an interruption, will restart dosing at a reduced dose and

will be titrated to the maintenance dose. Subjects randomized to BG00012 will receive a dose of 120 mg BID orally for 7 days followed by the maintenance dose of 240 mg BID. Subjects randomized to BIIB017 will be titrated to the target dose of 125 µg SC as follows: 63 µg on Day 1, 94 µg at Week 2, and 125 µg at Week 4. To ensure blinding across the 3 treatment groups, each subject will receive BG00012 or matching placebo administered orally BID and BIIB017 or matching placebo administered SC at the corresponding timepoints.

11.2.4. Subsequent Development of Additional Laboratory Abnormalities

Subjects who subsequently develop the same abnormal laboratory value at any other time during the study must permanently discontinue dosing with study treatment or alternative therapy, 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 resumed dosing after ALT returned to acceptable limits, and subsequently developed abnormal WBCs, the subject may have study treatment or alternative therapy withheld again. However, only 2 dosing interruptions are allowed for each subject.

Any subject who experiences abnormal laboratory results (that meet the criteria defined in Table 5 on a third occasion must permanently discontinue dosing for the remainder of the study.

11.2.5. Abnormal Urinalyses That Require Additional Evaluation

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

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

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

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

11.2.6. Treatment Schedule for Subjects With Abnormal Lymphocyte Count

11.2.6.1. Schedule for Subjects on Study Treatment or Alternative Therapy With Lymphocyte Count <LLN

Subjects who are on study treatment and who have a lymphocyte count <LLN will be followed every 4 weeks until the lymphocyte count is ≥LLN.

If subjects who are on study treatment have a lymphocyte count <500/mm^3, the 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.

Table 6: Lymphocyte Count Criteria Requiring Permanent Discontinuation of Study Treatment or Alternative Therapy

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 the lymphocyte count is <500/mm^3, the lymphocyte count should be closely monitored (at least every 4 weeks). If the lymphocyte count is <500/mm^3 for >24 weeks, study treatment or Tecfidera administered as alternative therapy must be permanently discontinued.

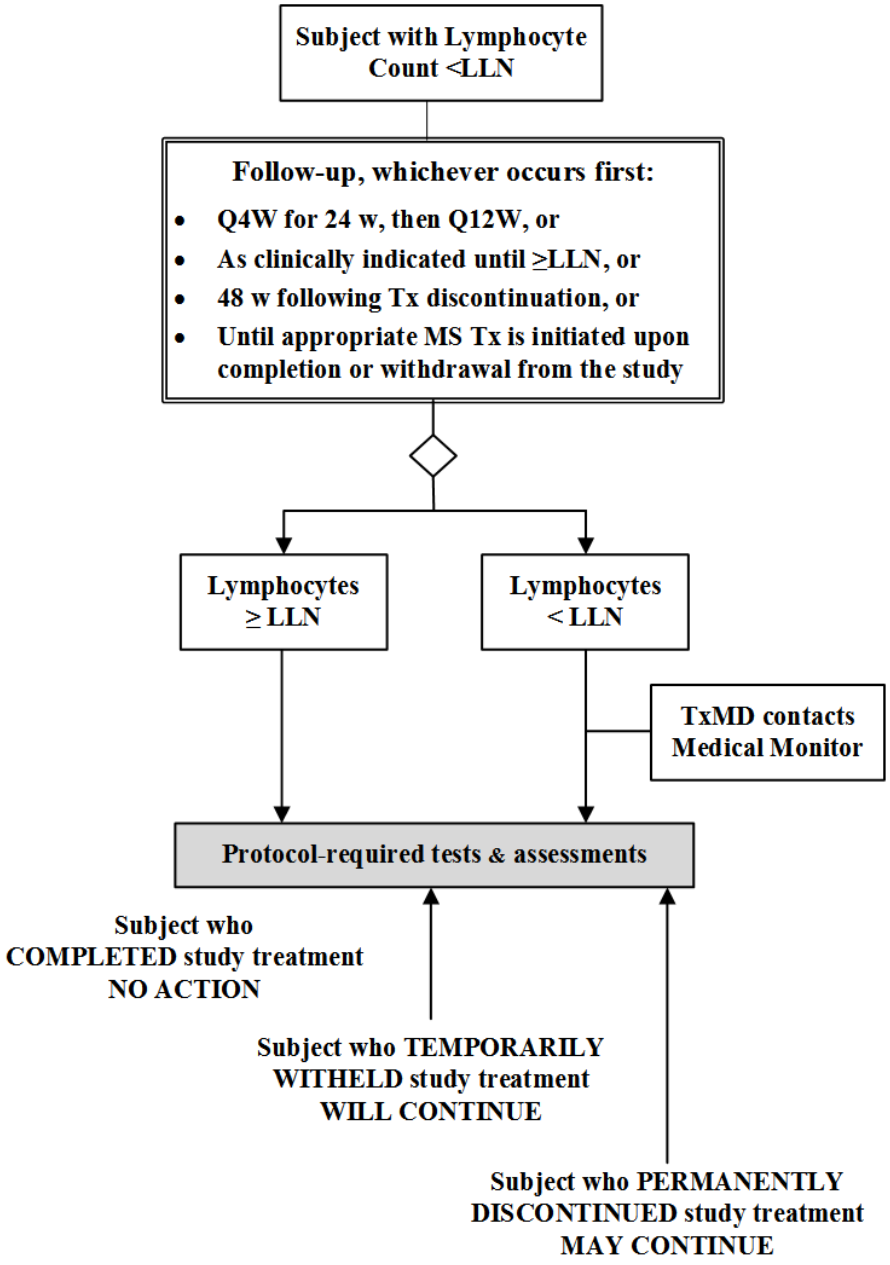
11.2.6.2. Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for any Reason and Have Lymphocyte Count <LLN

Subjects who complete the 96-week Treatment Period and who have a lymphocyte count <LLN will be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**), until the lymphocyte count is ≥LLN, or for 48 weeks following treatment discontinuation, whichever occurs sooner, or until the subject is initiated on the appropriate MS treatment, according to local standard of care, following study withdrawal/completion. If the lymphocyte count does not recover after 48 weeks, the treating neurologist should contact the Medical Monitor.

Subjects who temporarily withhold or permanently discontinue study treatment for any reason (see Section 11.2.2) and who have a lymphocyte count <LLN will continue protocol-required tests and assessments and also undergo lymphocyte follow-up every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**), until the lymphocyte count is ≥LLN, or for 48 weeks following treatment discontinuation, whichever occurs sooner, or until the subject is initiated on the appropriate MS treatment, according to local standard of care, following study withdrawal/completion. If the lymphocyte count does not recover after 48 weeks, the treating neurologist should contact the Medical Monitor.

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

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



DxMD, examining neurologist; **LLN**, lower-limit of normal; **MS**, multiple sclerosis; **Q2W**, every two weeks; **Q4W**, every 4 weeks; **Tx**, treatment; **TxMD,** treating neurologist or nurse.

11.3. Precautions

Not applicable.

11.4. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff. Compliance will be monitored by capsule count and syringe or auto-injector pen count conducted by study personnel at protocol-scheduled visits.

11.5. Concomitant Therapy and Procedures

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

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the subject's Baseline and last study visit.

11.5.1.1. Allowed Concomitant Therapy

Subjects should be instructed to contact their Investigators before taking any new medications, including nonprescription medications and herbal preparations.

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

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:

- Any alternative drug treatments directed toward the treatment of MS such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to INF-β [with the exception of study-assigned BIIB017], IFN-α, GA, natalizumab, alemtuzumab, cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, dimethyl fumarate, teriflunomide, 4-aminopyridine, fingolimod, or related products), with the exception of acute management of protocol-defined relapse (as described below).

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

- Any systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IVMP, except for protocol-defined treatment of relapses as described in Section 7.2.3. Steroids that are administered by nonsystemic routes (e.g., topical, inhaled) are allowed.

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

Subjects who receive any of these restricted medications without approval from the Medical Monitor will be required to permanently discontinue study treatment and will be withdrawn from the study as described in Section 10.2.

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 subject's Baseline and last study visit.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If BG00012 and BIIB017 are proven to be beneficial, all regulatory requirements regarding post-study access will be met.

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.

Study treatment kits will be identified by unique kit numbers on the clinical label. To ensure the appropriate treatment is provided to each subject, an interactive response technology (IRT) will be used to manage the dispensation of kits to subjects.

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 unless a written notification of an expiration date extension is provided by Biogen.

12.1.1. BG00012 Preparation

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

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

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

12.1.2. BG00012 Storage

BG00012 is to be stored at room temperature (15°C to 25°C or 59°F to 77°F), in a secured, locked area 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 and quantities), the date of destruction, and proof of destruction.

12.1.4. BG00012 Accountability

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

12.2. BIIB017

BIIB017 is supplied as a liquid in an auto-injector pen to deliver 0.5 mL of 0.25 mg/mL (125 µg dose) of 20 kDa mPEG-O-2-methylpropionaldehyde-modified human IFN β-1a in 20 mM acetic acid/sodium acetate buffer pH 4.8, 150 mM arginine hydrochloride, and 0.005% polysorbate 20.

BIIB017 is also supplied as a liquid in a prefilled-syringe (PFS) for titration dosing to deliver 0.5 mL of 0.13 mg/mL (63 µg dose) or 0.19 mg/mL (94 µg dose) of 20 kDa mPEG-O-2-methylpropionaldehyde-modified human IFN β-1a in 20 mM acetic acid/sodium acetate buffer pH 4.8, 150 mM arginine hydrochloride, and 0.005% polysorbate 20.

The label will include conditions for storage, kit number, and other pertinent information in accordance with local regulations such as Sponsor, expiration date, and a caution statement. BIIB017 should not be used after the expiration date unless a written notification of an expiration date extension is provided by Biogen.

12.2.1. BIIB017 Preparation

The individual preparing BIIB017 should carefully review the instructions provided in the DHA.

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

12.2.2. BIIB017 Storage

BIIB017 is to be stored at 2°C to 8°C (36°F to 46°F) in a temperature-monitored, secured, and locked refrigerator with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.2.3. BIIB017 Handling and Disposal

The Investigator must return all used and unused syringes and auto-injector pens of BIIB017 as instructed by Biogen unless approved for onsite destruction.

If any BIIB017 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.

12.2.4. BIIB017 Accountability

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

Unless otherwise notified, all syringes and auto-injector pens, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of BIIB017 supplied, dispensed, and subsequently destroyed, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

12.3. Placebo

The matched placebo for BG00012 will be supplied as enteric-coated microtablets in gelatin capsules (blue and white) for oral administration. DMF has been replaced in the placebo by lactose monohydrate to maintain the total weight.

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.

Placebo is to be stored under the same conditions as those for BG00012.

The matched diluent/placebo (20 mM acetic acid/sodium acetate pH 4.8, 150 mM arginine hydrochloride, and 0.005% polysorbate 20) for BIIB017 will be provided in a PFS, to deliver 0.5 mL.

Placebo is to be stored under the same conditions as those for BIIB017.

12.4. Additional Protocol-Designated Products

For the first 24 weeks of the study (starting at Baseline), all subjects will be instructed to take either acetaminophen (paracetamol) or ibuprofen prior to each injection and for the 24 hours following each injection at the recommended doses and frequencies per the local labels. If a subject is allergic to or intolerant of acetaminophen or ibuprofen, other NSAIDs such as naproxen may be administered at the recommended dose and frequency per the local labels. After the first 24 weeks of the study, acetaminophen, ibuprofen, or other NSAID treatment may be discontinued at the discretion of the Investigator.

Subjects may receive additional doses of acetaminophen, ibuprofen, or naproxen, 24 hours after injection as necessary for relief of IFN-related FLS. Sites should refer to the local labels for maximum daily dosages of these medications. Subjects should be instructed to contact the site if they require additional medication beyond the maximum daily dosage per the local labels.

For current and updated US Label Dosing Guidelines refer to the Food and Drug Administration website (www.fda.gov).

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 and BIIB017:

- Protocol-defined relapse
- [redacted]
- [redacted]

13.2. Radiological Efficacy Assessments

The following radiological efficacy assessments will be performed to evaluate the efficacy of BG00012 and BIIB017:

- Brain MRI scans with and without Gd
  - total Gd-enhancing lesions
  - new or newly enlarging T2 hyperintense lesions
  - [redacted]
  - new or newly enlarging T1 hypointense lesions
  - [redacted]

13.3. Additional Assessments

[redacted]

- [redacted]
- [redacted]

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 and BIIB017:

- AEs and SAEs
- [redacted]

14.2. Laboratory Safety Assessments

[redacted]

14.3. Study-Specific Safety Assessments

[redacted]

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 LAR 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 (i.e., BG00012 and BIIB017), 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 and Post-Treatment Visit is to be recorded on the CRF, 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 Post-Treatment 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 Post-Treatment 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 Post-Treatment 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, fax or email a completed SAE form to the following: [redacted].

Fax: See the Study Reference Manual

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 CRF. 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.

Appropriate personnel at Biogen will unblind SUSARs for the purpose of regulatory reporting. Biogen will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 3 months 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 the appropriate form within 24 hours of the study site staff becoming aware of the pregnancy to [redacted] (fax: see the Study Reference Manual; email: [redacted]).

The Investigator or study site staff must report the outcome of the pregnancy to [redacted].

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 CRF; 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 SABR 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 CRF.

15.4.3. Medical Emergency

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

15.4.3.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator and, if applicable, designated personnel at Biogen may access the subject's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study. The Investigator can contact Biogen or designee to discuss such situations.

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency or to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

Sexually active subjects of reproductive potential must practice effective contraception during the study and for 3 months after their last dose of study treatment. Investigators should advise subjects of the potential risks associated with pregnancy while taking BG00012 or BIIB017 and on the appropriate use of contraceptives (as defined below).

For the purposes of the study, 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/available).
- Female surgical sterilization (e.g., bilateral tubal ligation)

For males:

- Effective male contraception includes the use of condoms with spermicide

In addition, male subjects must not donate sperm from the Baseline Visit (Day 1) to at least 90 days after administration of the last dose of study treatment.

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, 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, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow up on the outcome.
- 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.
- 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.
- Report SAEs to local ethics committees, as required by local law.

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.

The study is conducted to evaluate the efficacy and safety profiles of BG00012 and BIIB017, both compared with placebo, in pediatric subjects with RRMS. Two separate sets of analyses will be performed for assessment of each active treatment. One will include subjects assigned to BG00012 and placebo, and the other will include subjects assigned to BIIB017 and placebo. Unless noted otherwise, analysis methods described in this section would apply to both sets of analyses.

The stratification factor (age [10 to ≤14 years of age and 15 to 17 years of age]) will be included in relevant statistical models.

16.1. Efficacy

16.1.1. Analysis Population

The primary efficacy analysis will include subjects in the efficacy population, defined as those who are randomized and receive at least 1 dose of study treatment (BG00012, BIIB017, or placebo). Subjects will be analyzed according to the treatment group to which they are randomized.

16.1.2. Methods of Analysis

In general, summary statistics will be presented. Continuous variables will be summarized using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group.

Baseline is defined as the closest nonmissing value prior to the first dose of study treatment, unless otherwise specified.

Statistical testing will be conducted at significance level of 0.05.

16.1.2.1. Analysis of the Primary Endpoint

The primary endpoint of this study is TTFR. Kaplan-Meier curves will be used to summarize the proportion of subjects achieving the primary endpoint over time. A Cox proportional hazards model will be used to compare the BG00012 group and the placebo group and the BIIB017 group and the placebo group. The model will be stratified by baseline age group and will include covariates for treatment, baseline relapse rate, baseline age, presence of Gd-enhancing lesions at Baseline, and baseline [redacted]. Baseline relapse rate will be defined as the number of relapses over the 2 years prior to study entry, divided by 2. The hazard ratio of BG00012 versus placebo

and BIIB017 versus placebo and the 95% confidence interval (CI) will be derived from the model.

Subjects who withdraw early without a relapse event for reasons unrelated to efficacy will be censored, and subjects who withdraw due to lack of efficacy will be considered as cases with an event at the time of withdrawal. Subjects who elect to start an alternative therapy following a protocol-defined event of disability progression will also be considered as cases with an event at time of confirmed disability progression.

16.1.2.2. Analysis of the Secondary Endpoints

MRI: Number of New or Newly Enlarging T2 Hyperintense Lesions at Weeks 48 and 96

The number of new or newly enlarging T2 hyperintense lesions will be summarized by treatment group and timepoint. Comparison between BG00012 group and placebo group and between BIIB017 group and placebo group at each timepoint will be made using the negative binomial regression model. The analysis model will be stratified by baseline age group and will include covariates for treatment and number of baseline T2 lesions. The rate ratio of BG00012 versus placebo and BIIB017 versus placebo and the 95% CI will be derived from the model.

Missing values for subjects who withdraw early will not be imputed. The MRI scan reads after subjects elect to start an alternative therapy following an event of relapse or disability progression will not be included in the summary or analysis.

MRI: Number of Gd-Enhancing Lesions at Baseline and at Weeks 48 and 96

The number of Gd-enhancing lesions will be summarized by treatment group and timepoint. Comparison between BG00012 group and placebo group and between BIIB017 group and placebo group at each timepoint will be made using a negative binomial regression model. The analysis model will be stratified by baseline age group and will include covariates for treatment and number of baseline Gd-enhancing lesions. The rate ratio of BG00012 versus placebo and BIIB017 versus placebo, and the 95% CI will be derived from the model.

Missing values for subjects who withdraw early will not be imputed. The MRI scan reads after subjects elect to start an alternative therapy following an event of relapse or disability progression will not be included in the summary or analysis.

Annualized Relapse Rate at Weeks 48 and 96

The number of relapses in each treatment group adjusted for the duration of study treatment before the start of alternative therapy will be annualized at Weeks 48 and 96. At each timepoint, the number of relapses will be analyzed by a negative binomial regression model. Logarithmic transformation of the time on study will be included as an independent variable in the model as the "offset" parameter. The model will be stratified by baseline age group and will include covariates for treatment, baseline relapse rate, baseline age, and baseline [redacted]. Baseline relapse rate will be defined as the number of relapses over the 2 years prior to study entry, divided by 2. The adjusted relapse rate from the negative binomial regression analysis will be presented for

each group. The rate ratio for BG00012 versus placebo and BIIB017 versus placebo and the 95% CI will also be derived from the model. Relapses that occur after subjects elect to start an alternative therapy following an event of relapse or disability progression will not be included in the summary or analysis.

16.1.2.3. Additional Endpoints Analysis

[redacted]

16.2. Pharmacokinetics

Not applicable.

16.3. Pharmacodynamics

Not applicable.

[redacted]

Not applicable.

16.5. Safety

16.5.1. Analysis Population

The safety population is defined as all subjects who receive at least 1 dose of study treatment. Subjects will be analyzed based on the actual treatment received.

The primary safety analyses of AEs, [redacted] will be performed based on the safety population during the period from the first dose of blinded treatment to the end of the blinded treatment. In general, safety data collected after subjects elect to start open-label BG00012 or an alternative therapy will be excluded from these primary summary analyses. However, supportive analyses on all safety data, including those collected during the period of treatment with open-label BG00012 or alternative therapies will be provided.

16.5.2. Methods of Analysis

Descriptive statistics and frequency tables will be used to summarize data. No formal statistical testing is planned.

16.5.2.1. Adverse Events

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

The incidence of treatment-emergent AEs will be tabulated by treatment group, severity, and relationship to study treatment. The tabular summaries will include incidence by system organ class and by preferred term. SAEs and AEs resulting in treatment discontinuation and/or study withdrawal will also be identified. For the analysis of incidence by severity, the occurrence of the AE with the greatest severity will be used, and a subject will be counted only once and only in the category of the greatest severity for each event. For the analysis of incidence by relationship to study treatment, the occurrence of the AE with the strongest relationship to study treatment will be used, and a subject will be counted only once and only in the category of the strongest relationship to study treatment for each event.

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

16.6.2. Methods of Analysis

[redacted]

[redacted]

[redacted]

16.7. Interim Analyses

Not applicable.

16.8. Sample Size Considerations

The primary endpoint of this study is TTFR. In the Phase 3 adult study of BG00012 (Study 109MS301), with the same endpoint, the reduction in the risk of relapse over 2 years while receiving BG00012 240 mg BID compared with placebo was estimated to be 50%. In the Phase 3 adult study of BIIB017 (Study 105MS301) with the same endpoint, the reduction in the risk of relapse over 1 year (the placebo-controlled period of this trial) while receiving BIIB017 125 µg every 2 weeks compared with placebo was estimated to be 39%. Based on the reported proportion of subjects who had a relapse in the Interferon beta 1-a arm of the PARADIGMS study (61.2%) [Chitnis 2018], and consistent with the understanding of pediatric MS, a higher relapse rate was observed in pediatric subjects compared to adult subjects. This is supported by internal data from BG00012 studies on younger adult (ages 18-25 years) subjects. Conservatively assuming that 75% of subjects in the placebo group will have their first relapse during the 2-year period, the study will have at least 80% power to detect a 50% and 39% reduction compared with placebo in the risk of relapse in the BG00012 and BIIB017 arms, respectively, when a total of 153 events (first relapses) have accrued. The type I error of each comparison will be controlled at 0.05. This 3-arm study will be conducted in a pediatric MS population to evaluate the efficacy and safety of BG00012 and BIIB017, each compared with the same placebo arm. The same goals could be achieved in 2 separate placebo-controlled studies. However, the 3-arm platform design will have fewer subjects exposed to placebo. With 2 comparisons to be made separately between different active treatments and placebo (BG00012 vs. placebo and BIIB017 vs. placebo), as in 2 separate studies, multiplicity adjustment is unnecessary. Taking into account a 2-year discontinuation rate of 15%, the study plans to randomize approximately 260 subjects (approximately 52 subjects randomized to BG00012, 104 subjects randomized to BIIB017, and 104 subjects randomized to placebo). The discontinuation rate will be monitored throughout the study, and discontinued subjects may be replaced by new subjects to achieve 80% power.

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's LAR (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 and the subject's LAR. The subject must be given sufficient time to consider whether to participate in the study.

The subject and LAR will be informed that race, ethnicity, and month and year of birth will be collected during the study (unless the collection is not permitted by applicable law or not approved by the governing ethics committee), and that those data will be used during the conduct and analysis of 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's LAR. 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).

During the study, the subject's race, ethnicity, and month and year of birth will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). Since it is not known whether the effects of the study treatment are influenced by race or ethnicity, this information will be of value in the analysis of safety. The month and year of birth information is necessary to confirm study eligibility, to facilitate clinical assessments (such as [redacted], where permitted), to employ age-dependent laboratory reference intervals, and to conduct the planned statistical analysis.

The subject will not be identified by name in the CRF or in any study report, 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) 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 screen any subjects prior to completion of a study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

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, CRFs 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 the oversight of all administrative aspects of this study handled by the CRO [redacted], including but not limited to study initiation, monitoring, management of AEs, and data management.

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, monitoring, medical support, 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. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool supported by iMedidata Rave and configured by [redacted]

19.1.4. Central Laboratories for Laboratory Assessments

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

19.1.5. Central Facility for Other Assessments

All of the MRI scans with and without Gd will be evaluated at a central MRI reading center. All investigational sites will be required to send a test scan of a healthy volunteer or a subject with MS to the MRI reading center for evaluation in order to ensure that the site's scanning techniques are appropriate. This review will take place before the investigational site is permitted to enroll any subjects into the study.

MRI digital data should be sent by mail or via the network to a secure file transfer protocol (FTP) server. Other methods of data transfer may be acceptable on a case-by-case basis (the Clinical Monitor will provide specific MRI data shipping instructions prior to the start of enrollment at each site).

Additional and more detailed MRI scans with and without Gd procedures and protocols are included in the study MRI manual.

19.2. Study Committees

19.2.1. Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) will be formed to review safety data and alert and/or make recommendations to the Advisory Committee about any existing or potential problems. All SAEs will be forwarded to the DSMC as monthly cumulative SAE listings. In addition, the DSMC will be able to access unblinded data as needed.

19.2.2. Steering (Advisory) Committee

A Steering (Advisory) Committee will be formed to provide scientific and medical direction for the study. The Steering Committee will meet at regular intervals to monitor subject accrual and to discuss recruitment, external competitive environment and mitigation strategies.

Members of the Steering Committee will include the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen (and/or their designees), and external experts. Biogen will designate one of the external experts to be the Chairperson of the Steering Committee.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the 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 similar 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 one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to, the Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or subject enrollment; or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, 3-Arm, Parallel-Group Study in Pediatric Subjects Aged 10 Through 17 Years to Evaluate the Efficacy and Safety of BG00012 and BIIB017 for the Treatment of 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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AMENDMENT SUMMARY

Biogen Protocol 800MS301

A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, 3-Arm, Parallel-Group Study in Pediatric Subjects Aged 10 Through 17 Years to Evaluate the Efficacy and Safety of BG00012 and BIIB017 for the Treatment of Relapsing-Remitting Multiple Sclerosis

Version 3

Date: 09 August 2018

EUDRA CT Number: 2018-000516-22

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

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 800MS301 is to clarify the level of detail and purpose of date-of-birth (DOB) information being collected for the subjects enrolled in the study.

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

Section 17.4, Subject Data Protection

Now reads:

During the study, **the** subject**'**s~~'~~ race**,** ~~and~~ ethnicity**,** and ~~full date~~**month and year** of birth will be collected~~,~~ **(**unless the collection is not permitted by applicable law or not approved by the governing ethics committee**)**. ~~These data will be used in the analysis of the safety profile of the study treatment.~~**Since** ~~I~~**i**t is **not** ~~un~~known whether the effects of the study treatment are influenced by race or ethnicity**, this information will be of value in the analysis of safety. The month and year of birth information is necessary to confirm study eligibility, to facilitate clinical assessments (such as [redacted], where permitted), to employ age-dependent laboratory reference intervals, and to conduct the planned statistical analysis**.

Rationale: This study involves the treatment of pediatric subjects with relapsing-remitting multiple sclerosis between 10 and 17 years of age, inclusive, for up to 96 weeks. The collection of full DOB information was determined to be inconsistent with standard Biogen practice and subject to restriction in many countries as a matter of personal privacy; however, the collection of both the month and year of birth is necessary to conduct and analyze the study properly.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 4.3.1, Administration of Study Treatment

Change: The reference to "caregiver" was deleted.

Now reads:

To ensure blinding across the 3 treatment groups, each subject will receive BG00012 or placebo capsules administered orally BID and BIIB017 or placebo injection administered SC every 2 weeks. Subjects can either swallow the capsules whole (preferred) or open the capsules and mix with food immediately prior to consumption. If the subject is unable to self-administer the SC treatment, the ~~caregiver or~~parent will be allowed to administer the treatment.

Rationale: The subject's legally authorized representative (LAR; i.e., parent or legal guardian) has the authority and bears the responsibility for all decisions and actions regarding the subject's participation in the study. This includes compliance with the administration of study treatment, which is expected to be done by the subject or the parent. Any caregiver who may be involved in facilitating management of the subject's participation does so at the discretion of the LAR.

This change also affects Section 4.2, Schedule of Activities (Table 1: Study Activities and Assessments, footnote 17); Section 7.2.1, Relapses; and Section 15, Safety Definitions, Recordings, Reporting, and Responsibilities.

Section 8.1, Inclusion Criteria

Change: Criterion 1 was revised.

Now reads:

1. Ability of **a legally authorized representative (LAR;** parent~~s~~ or legal guardian~~s~~**)** 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 ~~parent's or guardian's~~ **LAR's** consent, as appropriate, per local regulations.

Rationale: The obligation of the LAR, not the subject, to provide written informed consent was clarified, given that the subjects participating in this study have not reached the age of majority at the time of enrollment.

This change also affects Section 9.1, Screening and Enrollment; Section 15, Safety Definitions, Recording, Reporting, and Responsibilities; and Section 17.3, Subject Information and Consent.

Section 8.2, Exclusion Criteria

Change: Criterion 17 was revised.

Now reads:

- Prior treatment that might influence growth, including but not limited to methylphenidate hydrochloride, thyroid hormone, growth hormone, anabolic steroids, calcitonin, estrogens, progestins **(with the exception of medication used for contraception)**, bisphosphonates, anticonvulsants, or phosphate-binding antacids.

Rationale: The general exclusion of prior or concomitant treatment with progestins does not apply to subjects using oral contraceptives during the study.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- The List of Abbreviations was updated.
- Figures 1, 2, and 3 were completely revised to improve completeness and readability.
- Table 1 was revised to clarify that the Week 2 and Week 4 contacts with the subject provide the option for a clinic visit or telephone call.
- Table 2 was revised to move the Early Withdrawal Visit column from the leftmost to the rightmost position.

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AMENDMENT SUMMARY

Biogen Protocol 800MS301

A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, 3-Arm, Parallel-Group Study in Pediatric Subjects Aged 10 Through 17 Years to Evaluate the Efficacy and Safety of BG00012 and BIIB017 for the Treatment of Relapsing-Remitting Multiple Sclerosis

Version 2.0

Date: 15 June 2018

Version 2.0 of the protocol has been prepared for this amendment, which supersedes Version 1.0.

PRIMARY REASON FOR AMENDMENT

The primary reasons for this amendment to Protocol 800MS301 are:

a) To exclude those subjects from further follow-up, who have a low lymphocyte count following study withdrawal/completion, should they be initiated on appropriate MS treatment, according to local standard of care.

b) Provision of open-label access to BG00012 (Tecfidera) for subjects who experience a confirmed relapse at any point during the study or who have a high lesion burden on magnetic resonance imaging (MRI) at Week 48 until the end of their scheduled participation in the study if this is considered suitable by the treating neurologist.

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

a) Section 7.1, Study Overview

Now reads:

Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <lower limit of normal (LLN) will be followed at least every 4 weeks for 24 weeks, then every 12 weeks (unless clinically indicated more often or at the Investigator's discretion) until the lymphocyte count is ≥LLN, or for 48 weeks following treatment discontinuation, whichever is sooner**, or until the subject is initiated on the appropriate MS treatment, according to local standard of care, following study withdrawal/completion**.

Rationale: The scientific purpose of monitoring lymphocyte count in subjects who have levels <LLN at the end of study completion or treatment interruption/discontinuation was to gain information on how long lymphocyte recovery takes after stopping BG00012. Subjects who have a low lymphocyte count following study withdrawal/completion and then continue to receive BG00012 are being excluded from further follow-up because reconstitution of lymphocytes will not occur if a subject continues on BG00012. In addition, if a subject is placed on BIIB017 or another disease-modifying therapy, it will not be possible to assess lymphocyte recovery time as the data will be confounded. Hence, any affected subjects would have been exposed to unnecessary blood tests without any scientific knowledge being gained.

This change also affects Section 4.2, Schedule of Activities, Table 2; Section 7.3.3, Follow-Up; and Section 11.2.6.2, Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for Any Reason and Have a Lymphocyte Count <LLN.

b) Section 7.1, Study Overview

Now reads:

~~If a confirmed relapse or disability progression occurs, the subject will be eligible to receive appropriate alternative therapy, along with any requisite safety monitoring, at the discretion of the treating neurologist and will be allowed to remain in the study. Investigators can choose to offer alternative DMTs according to local standard of care.~~

During the study, subjects who have a confirmed relapse or disability progression or a high lesion burden on MRI at Week 48 (defined as ≥9 new/enlarged T2 lesions) will have the option of switching to an alternative therapy in accordance with local practices, or open-label BG00012 (Tecfidera), at the discretion of the Investigator. Subjects will discontinue blinded study treatment when they switch to an alternative therapy or open-label BG00012. Subjects who are switched to an alternative therapy or open-label BG00012 will remain in the study to complete the scheduled visits, along with any requisite safety monitoring. Open-label BG00012 will only be provided until the subject completes or withdraws from the study or according to local regulatory requirements.

If a subject receives **open-label BG00012 or** an alternative therapy, they should be assessed at the **Open-Label BG00012/**Alternative Therapy Visit within ~~2~~4 weeks of switching.

Section 7.2.3, MS Relapses, Treatment, and Alternative MS Therapy

Now reads:

During the study, s~~S~~ubjects **who have a confirmed relapse or disability progression or high lesion burden on MRI at Week 48 (defined as ≥9 new/enlarged T2 lesions)** will have the option of switching to an alternative therapy in accordance with local practices, **or open-label BG00012,** at the discretion of the Investigator. Subjects will discontinue **blinded** study treatment when they switch to an alternative therapy **or open-label BG00012**~~due to a relapse or disability,~~**. Subjects who are switched to an alternative therapy or open-label BG00012** will~~but can~~ remain in the study to complete the scheduled visits**, along with any requisite safety monitoring. Open-label BG00012 will only be provided until the subject completes or withdraws from the study or according to local regulatory requirements**.

Rationale: Patients will be allowed to receive open-label BG00012 (Tecfidera) following a confirmed relapse or disability progression or who have a high lesion burden on MRI at Week 48 and if they continue in the study for the continued monitoring of safety and efficacy. Where Investigators think it is more appropriate, subjects may switch to alternative therapies and are allowed to remain in the study. The rationale for providing BG00012 is that it has an established safety and efficacy profile in the adult population and is relatively easy to administer, not requiring SC injections in the pediatric population. Furthermore, subjects will not be unblinded, thus, it is preferable to continue subjects on open-label therapy with the treatment demonstrated to have higher efficacy than interferons in the adult population.

This change also affects Section 4.1, Study Schematic, Figure 1; Section 4.2, Schedule of Activities, Table 2; Section 7.2.1, Relapses; Section 7.2.2, Definition of Disability Progression; Section 7.3.2, Treatment; and Section 7.3.3, Follow-Up.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 4.2, Schedule of Events

Change: Figure 1 and Table 1 have been amended to make clinic visits at Weeks 2 and 6 optional, if patients need assistance with their injections.

Table 1 Column Headings for Weeks 2 and 6 now read:

Wk 2 ±2 D **(Optional 'Phone Calls)** and Wk 6 ±2 D **(Optional 'Phone Calls)**

[redacted]

Rationale: This change was made to reduce the burden of additional clinic visits when not absolutely required.

Section 4.2, Schedule of Events

Change: The footnotes relating to vital signs have been amended with the provision of optional 'phone calls at Weeks 2 and 6, as referenced above. In addition, provisions have been included for home visits in the event that subjects need assistance with their injections, where possible.

Now reads as follows for Table 1:

[redacted]

Rationale: This change was made to reduce the burden of additional clinic visits when not absolutely required.

Section 4.2, Schedule of Events

Change: The row and associated footnote relating to the requirement for additional consent prior to performing any unscheduled assessments has been deleted as this was initially included in error.

Now reads as follows for Table 2:

~~[5]A written, signed informed consent form is to be obtained prior to performing any tests or assessments. Subjects must re-consent at each protocol-defined clinical relapse and/or disability progression during study, if applicable.~~

Rationale: This change was made because of an original error in the protocol.

Section 4.3.2, Blood Volumes

Change: The blood volumes have been amended as follows.

Table 3: Blood Volumes by Visit

	Screening Visit	**Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Treatment Period**											**Post-Treatment Visit**
Week	**(Within 6 Weeks of Baseline)**	**Baseline Visit (Day 1)**	**Wk 4 ±2 D**	**Wk 8 ±7 D**	**Wk 12 ±7 D**	**Wk 24 ±7 D**	**Wk 36 ±7 D**	**Wk 48 ±7 D**	**Wk 60 ±7 D**	**Wk 72 ±7 D**	**Wk 84 ±7 D**	**Wk 96 ±7 D**	**Wk 100 ±7 D**
Blood draw volume (mL)	**11.0**~~8.0~~	**14.0**~~7.0~~	**5.5** ~~8.0~~	**14.0** ~~6.0~~	7.0	**15.5** ~~7.0~~	**7.0**~~6.0~~	**15.5** ~~7.0~~	**7.0**~~6.0~~	**15.5** ~~8.0~~	**7.0** ~~6.0~~	**15.5** ~~7.0~~	**7.0**~~5.0~~

Table 4: Blood Volumes by Visit (Unscheduled Visits)

	Early Withdrawal Visit	**Open-Label BG00012/Alternative Therapy Visit (Within 4 Weeks after Switch if next Study Visit not Within 4 Weeks)**	**Lymphocyte Follow-Up Visit**	**Unscheduled Relapse Assessment Visit**
Blood draw volume (mL)	**15.5**~~6.0~~	**7.0**~~6.0~~	**2.0**~~1.2~~	**7.0**~~5.0~~

Rationale: This change was made because of an original error in the protocol.

Section 7.1, Study Overview

Change: Text has been amended to make clinic visits at Weeks 2 and 6 optional, if patients need assistance with their injections.

Now reads:

Clinic visits will occur at Day 1 and at Weeks ~~2,~~ 4, ~~6,~~ 8, 12, 24, 36, 48, 60, 72, 84, and 96. **Clinic visits at Weeks 2 and 6 are optional and, if not conducted, will occur by 'phone.**

Rationale: This change was made to reduce the burden of additional clinic visits when not absolutely required.

Section 7.3.2, Treatment

Change: Text has been amended to make clinic visits at Weeks 2 and 6 optional, if patients need assistance with their injections and to include additional visits for patients switching to open-label BG00012.

Now reads:

Eligible subjects will report to the study site to receive study treatment at Baseline (Day 1) and at Weeks ~~2,~~ 4, ~~6,~~ 8, 12, 24, 36, 48, 60, 72, and 84. **Clinic visits at Weeks 2 and 6 are optional and, if not conducted, will occur by 'phone.** Subjects will receive treatment for 96 weeks. Subjects who switch to **open-label BG00012 or** an alternative therapy and who are assessed at an **Open-Label BG00012**/Alternative Therapy Visit will then follow the same schedule for assessments as subjects remaining on their original study treatment.

Rationale: This change was made to reduce the burden of additional clinic visits when not absolutely required.

Section 8.1, Inclusion Criteria

Change: The text of Inclusion Criterion #6 has been amended to describe the options for the relevant conditions and to include the definition of relapse.

Now reads:

6. Must have experienced ≥1 relapse in the 12 months prior to randomization (Day 1)**, or must have evidence of asymptomatic disease activity (Gd-positive lesions) seen on MRI in the 6 months prior to randomization (Day 1),** or must have ≥2 relapses in the 24 months prior to randomization (Day 1). **Relapse is defined as the occurrence of a clinical demyelination event regardless of whether the event is a first (initial) or subsequent (recurrent) demyelinating event.**

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

Section 19.2.2, Steering (Advisory) Committee

Change: A new section has been inserted to detail the purpose and composition of a Steering Committee for study oversight.

Now reads:

A Steering (Advisory) Committee will be formed to provide scientific and medical direction for the study. The Steering Committee will meet at regular intervals to monitor subject accrual and to discuss recruitment, external competitive environment, and mitigation strategies.

Members of the Steering Committee will include the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen (and/or their designees), and external experts. Biogen will designate one of the external experts to be the Chairperson of the Steering Committee.

Rationale: This change is required to confirm with the accompanying reference in Section 19.2.1, Data Safety Monitoring Committee, to provide suitable oversight and direction for the study.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- With the license approval of Gilenya (fingolomid) for the pediatric population, references to no approved MS therapies for the pediatric population have now been amended to limited availability of MS therapies for this population. This amendment affects the Study Synopsis, Study Rationale; Section 5.2, Current Therapies for Multiple Sclerosis; Section 5.4, Study Rationale; and Section 5.5.1, Rationale for Comparator/Reference Product or Placebo.
- The number of sites for this study has been increased from approximately 34 sites to approximately 50 sites. This amendment affects the Study Synopsis, Study Location; and Section 7.1, Study Overview.
- Schedule 4.2, Schedule of Activities, Table 1 has been amended to delete the requirement for antibody sampling at Week 12.
- Schedule 4.2, Schedule of Activities, Tables 1 and 2, footnotes 3 and 4, respectively, have been amended to remove the level of detail regarding stadiometry measurements. **Now reads:** Height should be measured using stadiometry and recorded to the nearest 10th of a centimeter. ~~The stadiometer should be calibrated within 4 hours of measurement. Subjects should not be wearing socks, shoes, or a hat during measurement. Measurements should be made only by personnel trained in stadiometry and calibration procedures. It is recommended that the same site personnel measure the subject at every visit and that the personnel remain blinded to the subject's treatment assignment. Visits should be scheduled so that measurements can be taken at approximately the same time of day throughout the study.~~
- [redacted]
- [redacted]

- Section 4.2, Schedule of Activities, Tables 1 and 3 have been amended to extend the time window for clinic visits at Week 8 onward to ±7 days rather than ±5 days to ease the burden on parents and subjects and allow for greater flexibility in scheduling.

- Section 4.2, Schedule of Activities, Table 2, footnote 1 has been deleted as this is not applicable. **Now reads:** ~~[1]Tests and assessments must be completed prior to study treatment administration and/or distribution unless otherwise specified.~~

- Section 4.2, Schedule of Activities, Table 2 has been amended to delete the row referencing dispensing of treatment, as this does not take place at unscheduled visits.

- Section 4.3.3, Site Personnel has been amended because, in some countries, EDSS-certified raters are not necessarily neurologists. **Now reads:** ~~Both the treating neurologist and the examining neurologist must have a minimum of 2 years of neurology specialty training and be able to make at least a 1-year commitment to the study.~~ … The examining neurologist **or EDSS-certified rater** will be responsible for the following:

- Section 7.2.3, MS Relapses, Treatment, and Alternative MS Therapy, has been further amended to clarify that open-label BG00012 will only be provided until study completion or withdrawal. **Now reads:** Subjects will have the option of switching to an alternative therapy in accordance with local practices at the discretion of the Investigator **or open-label BG00012**. Subjects will discontinue study treatment when they switch to an alternative therapy **or open-label BG00012** due to a relapse or disability **(including high MRI disease activity at Week 48 [defined as ≥9 new/enlarged T2 lesions]). Subjects who are switched to alternative therapy are allowed to** ~~but can~~ remain in the study to complete the scheduled visits. **Open-label BG00012 will only be provided until the subject completes or withdraws from the study or according to local regulatory requirements.**

- Section 8.1, Inclusion Criteria: Inclusion Criterion #2 has been amended to allow for country-specific requirements relating to the minimum age. **Now reads:** Aged 10 to 17 years old, inclusive, at the time of informed consent. **The minimum age can be older than 10 years as required by country-specific regulations and/or local ethics committees.**

- Section 8.2, Exclusion Criteria: Exclusion Criterion #2 has been amended to remove the reference to historical disorders mimicking MS, as only current disorders are considered to be of an exclusionary nature. **Now reads:** ~~History of d~~Disorders mimicking MS, such as other demyelinating disorders (e.g., acute disseminated encephalomyelitis), systemic autoimmune disorders (e.g., Sjögren's disease and lupus erythematosus), metabolic disorders (e.g., dystrophies), and infectious disorders.

- Section 8.2, Exclusion Criteria: Exclusion Criterion #8 has been amended to clarify the definition of severe depression. **Now reads:** History of suicidal ideation within 3

months prior to randomization (Day 1) or an episode of severe depression within 3 months prior to randomization (Day 1). Severe depression is defined as an episode of depression that requires hospitalization or **is otherwise regarded as severe by** ~~at the discretion of~~ the Investigator.

- A typographical error has been corrected in Section 8.2, Exclusion Criteria: Exclusion Criterion #20, which **now reads:** History of drug or alcohol abuse (as **determined**~~defined~~ by the Investigator) within 2 years prior to randomization (Day 1).

- Section 8.2, Exclusion Criteria: Exclusion Criterion #23 has been amended to allow for the re-screening of subjects. **Now reads:** Previous **randomization**~~participation~~ in this study.

- Section 9.2, Randomization and Registration of Subjects has been amended to include details regarding stratification, which were previously missing. **Now reads:** Subjects will be randomized in a 1:2:2 ratio to receive BG00012:BIIB017:placebo. **Subjects will be stratified by age (10 to ≤14 years of age and 15 to 17 years of age) and by site.**

- Section 9.3, Blinding Procedures: Additional text inserted to allow for the disclosure of treatment assignments at the conclusion of the study. **Now reads: At the end of the study (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, Biogen will provide the randomization codes to Investigators, who then can inform their subjects about the treatment received.**

- Section 10.1, Discontinuation of Study Treatment has been amended to clarify the definition of severe depression. **Now reads:** Severe depression is defined as an episode of depression that requires hospitalization or **is otherwise regarded as severe by** ~~at the discretion of~~ the Investigator.

- Section 10.1, Discontinuation of Study Treatment has been amended to provide guidance in the event of a seizure or suspected seizure. **Now reads: In the event of a subject experiencing a seizure or suspected seizure during the study, they should be managed as per local clinical guidelines/standard medical care. The Investigator should re-evaluate whether the subject should continue in the study.**

- Section 11.2.3, Resumption of Study Treatment Dosing has been amended to provide clarification regarding the resumption of study treatment whilst maintaining study blinding. **Now reads:** Subjects randomized to BG00012 will receive a dose of 120 mg BID orally for 7 days followed by the maintenance dose of 240 mg BID. Subjects randomized to BIIB017 will be titrated to the target dose of 125 µg SC as follows: 63 µg on Day 1, 94 µg at Week 2, and 125 µg at Week 4. **To ensure blinding across the 3 treatment groups, each subject will receive BG00012 or**

matching placebo administered orally BID and BIIB017 or matching placebo administered SC at the corresponding timepoints.

- Section 11.4, Compliance has been amended to include reference to the auto-injector pen, which is also provided for study treatment BIIB017. This amendment also affects Section 12.2, BIIB017; Section 12.2.1, BIIB017 Preparation; Section 12.2.3, BIIB017 Handling and Disposal; and Section 12.2.4, BIIB017 Accountability.

- [redacted]

- References to [redacted] have been amended to [redacted] in Section 15.3.3, Immediate Reporting of Serious Adverse Events; Section 15.4.1, Pregnancy; Section 17, Ethical Requirements; Section 19.1, External Contract Organizations; and Section 19.1.3, Electronic Data Capture.

- Section 16, Statistical Methods and Determination of Sample Size has been amended to include provisions for stratification and **now reads: The stratification factor (age [10 to ≤14 years of age and 15 to 17 years of age]) will be included in relevant statistical models.**

- Section 16.1.1, Analysis Population has been amended as the efficacy analysis population is not strictly the intent-to-treat population. **Now reads:** The primary efficacy analysis will include subjects in the **efficacy population**~~intent-to-treat (ITT) population~~, defined as those who are randomized and receive at least 1 dose of study treatment (BG00012, BIIB017, or placebo). ~~Following the ITT principle, s~~**S**ubjects will be analyzed according to the treatment group to which they are randomized.

- Section 16.1.2.1, Analysis of the Primary Endpoint has been amended to include provisions for stratification and **now reads:** The model **will be stratified by baseline age group and** will include **covariates**~~a term~~ for treatment, ~~and will be adjusted for the~~ baseline relapse rate, baseline age, presence of Gd-enhancing lesions at baseline, and baseline [redacted].

- Section 16.1.2.2, Analysis of the Secondary Endpoints (MRI: Number of New or Newly Enlarging T2 Hyperintense Lesions at Weeks 48 and 96) has been amended to include provisions for stratification and **now reads:** The analysis model will **be stratified by baseline age group and will** include **covariates**~~a term~~ for treatment ~~group~~ and ~~for the~~ number of baseline T2 lesions.

- Section 16.1.2.2, Analysis of the Secondary Endpoints (MRI: Number of Gd-Enhancing Lesions at Baseline and at Weeks 48 and 96) has been amended to include provisions for stratification and **now reads:** Comparison between BG00012 group and placebo group and between BIIB017 group and placebo group at each timepoint will be made using **a negative binomial**~~multiple logistic~~ regression **model**. The analysis model will **be stratified by baseline age group and will** include **covariates**~~a term~~ for treatment and ~~for the~~ number of baseline Gd-enhancing lesions. The **rate**~~odds~~ ratio of BG00012 versus placebo and BIIB017 versus placebo, and the 95% CI will be derived from the model.

- Section 16.1.2.2, Analysis of the Secondary Endpoints (Annualized Relapse Rate at Weeks 48 and 96) has been amended to include provisions for stratification and **now reads:** The model will **be stratified by baseline age group and will** include **covariates**~~a term~~ for treatment, ~~and will be adjusted for~~ baseline relapse rate, baseline age, and baseline [redacted].

- Section 16.5.1, Analysis Population has been amended to provide further clarification regarding the safety analysis population. **Now reads:** The safety population is defined as all subjects who receive at least 1 dose of study treatment. **Subjects will be analyzed based on the actual treatment received.**

  The **primary** safety analyses of AEs, [redacted] will be performed based on the safety population **during the period from the first dose of blinded treatment to the end of the blinded treatment**~~, whether or not subjects have been on an alternative therapy following an event of protocol-defined relapse or disability progression~~. In general, safety data collected after subjects elect to start **open-label BG00012 or** an alternative therapy will be excluded from these **primary** summary analyses. However, **supportive analyses on** all safety data, including those collected during the period of treatment with **open-label BG00012 or** alternative therapies, will be **provided**~~reported in subject listings~~.

- Section 16.8, Sample Size Considerations has been amended as there was an initial error in the study protocol. **Now reads:** Assuming that 59.6% of subjects in the placebo group will have their first relapse during the 2-year period, the study will have at least 80% power to detect a 50% and 39% reduction compared with placebo in the risk of relapse in the BG00012 and BIIB017 arms, respectively, when a total of ~~148~~**156** events (first relapses) have accrued.

- Section 17.4, Subject Data Protection has been amended to explicitly state that race, ethnicity, and date of birth will be obtained, where allowed for by local regulations. **Now reads: During the study, subjects' race and ethnicity and full date of birth will be collected, unless the collection is not permitted by applicable law or not approved by the governing ethics committee. These data will be used in the analysis of the safety profile of the study treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity.**

- Typographical errors and formatting were corrected.