STATISTICAL ANALYSIS PLAN

Version No.: 1.0

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Author: [redacted], Ph.D.

Study 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

Name of Study Treatment: BG00012 (dimethyl fumarate; Tecfidera®); BIIB017 (peginterferon β-1a; Plegridy®)

Protocol No.: 800MS301/ NCT03870763

Study Phase: 3

APPROVAL

This document has been reviewed and approved by:		
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VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
0.1 (Stable SAP)	14-MAY-2021	N/A
1.0 (Final SAP)	03-MAY-2022	N/A

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BID	twice daily
BPM	beats per minute
[redacted]	[redacted]
[redacted]	[redacted]
CRF	case report form
DMF	dimethyl fumarate
[redacted]	[redacted]
[redacted]	[redacted]
Gd	gadolinium
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HIV	human immunodeficiency virus
ICF	informed consent form
[redacted]	[redacted]
ITT	intent-to-treat
IV	intravenous
IVMP	intravenous methylprednisolone
LAR	legally authorized representative
LLN	lower limit of normal

Abbreviation	Definition
MRI	magnetic resonance imaging
MedDRA	Medical Dictionary for Regulatory Affairs
MS	multiple sclerosis
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic
[redacted]	[redacted]
PEG	polyethylene glycol
PK	pharmacokinetic
PRO	Patient-reported Outcome
[redacted]	[redacted]
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SC	subcutaneous
[redacted]	[redacted]
TTFR	time to first relapse
WHO	World Health Organization

1. Introduction

This SAP is associated with the BLAST study (800MS301) of BIIB917 (Tecfidera) and BG00012 (Plegridy). It is based on version 4 of the study protocol, dated 06-NOV-2020. This is the final SAP for the study and is intended to outline the basic planned analyses at the time of its writing.

The BLAST study was a randomized multicenter double-blind and double-dummy placebo-controlled three arm parallel group study to evaluate the efficacy and safety of BG00012 and BIIB017 in pediatric subjects with Relapsing-Remitting Multiple Sclerosis (RRMS).

2. Study Overview

This was 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.

Unless stated otherwise below, the term *summary statistics* refers to the computation of the mean, standard deviation, median, minimum, and maximum.

2.1. Study Objectives and Endpoints

Study Primary Objective

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

Study Primary Endpoint

The primary endpoint related to this objective was the Time-to-First Relapse (TTFR).

Study Secondary Objectives

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of BG00012 and BIIB017.
- To assess the effect of BG00012 and BIIB017, both compared to placebo, on additional clinical and radiological measures of disease activity.

Study Secondary Safety Endpoints

Occurrence of adverse events (AEs) and serious adverse events (SAEs). 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.

Additional Objectives and Endpoints

[redacted]

2.2. Study Design

This was a randomized, multicenter, double-blind, and double-dummy placebo-controlled three 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 (inclusive) with a diagnosis of RRMS as defined by the revised consensus definition for pediatric MS (Krupp LB, 2013), (Polman CH, 2011) were to be enrolled at approximately 50 sites globally. Eligible subjects were randomized within 6 weeks of screening. At least 25% of subjects were to be no more than 14 years of age. Subjects were stratified by age (10 to $\leq$ 14 years of age and 15 to 17 years of age) and by site. Subjects were randomized in a 1:2:2 ratio to treatment with placebo, BG00012, BIIB017, respectively. See the Study Activities schedule below for details on study visits. Visits in Week 2 and Week 6 were conducted in-person (optional) or telephonic. Subjects randomized to BG00012 received a starting dose of 120 mg BID orally (twice daily) for 7 days followed by a maintenance dose of 240 mg BID orally. Subjects randomized to BIIB017 were titrated to the target dose of 125 mg: 63 mg on Day 1, 94 mg at Week 2, and 125 mg at Week 4. Once subjects reached the 125 mg target dose, they continued with BIIB017 125 mg subcutaneously (SC) administered every two weeks for the remainder of the study. To ensure blinding across the treatment groups all subjects received BG00012 (or placebo) administered orally BID and BIIB017 (or placebo) administered SC every two weeks.

An Unscheduled Relapse Visit occurred 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 were treated at the treating neurologist's discretion with intravenous methylprednisolone (IVMP) at any time from Baseline to Week 100. Such treatment did not affect the subject's eligibility to continue in the study. The primary endpoint of the study was the TTFR: therefore, subjects were required to remain on the assigned blinded treatment until they experience their first protocol-defined relapse or disability progression.

During the study, subjects who had a confirmed relapse or disability progression or high lesion burden on MRI at Week 48 (defined as $\geq$9 new/enlarged T2 lesions) had 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 discontinued blinded study treatment when they switch to an alternative therapy or open-label BG00012. Subjects who were

switched to an alternative therapy or open-label BG00012 remained in the study to complete the scheduled visits, along with any requisite safety monitoring.

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

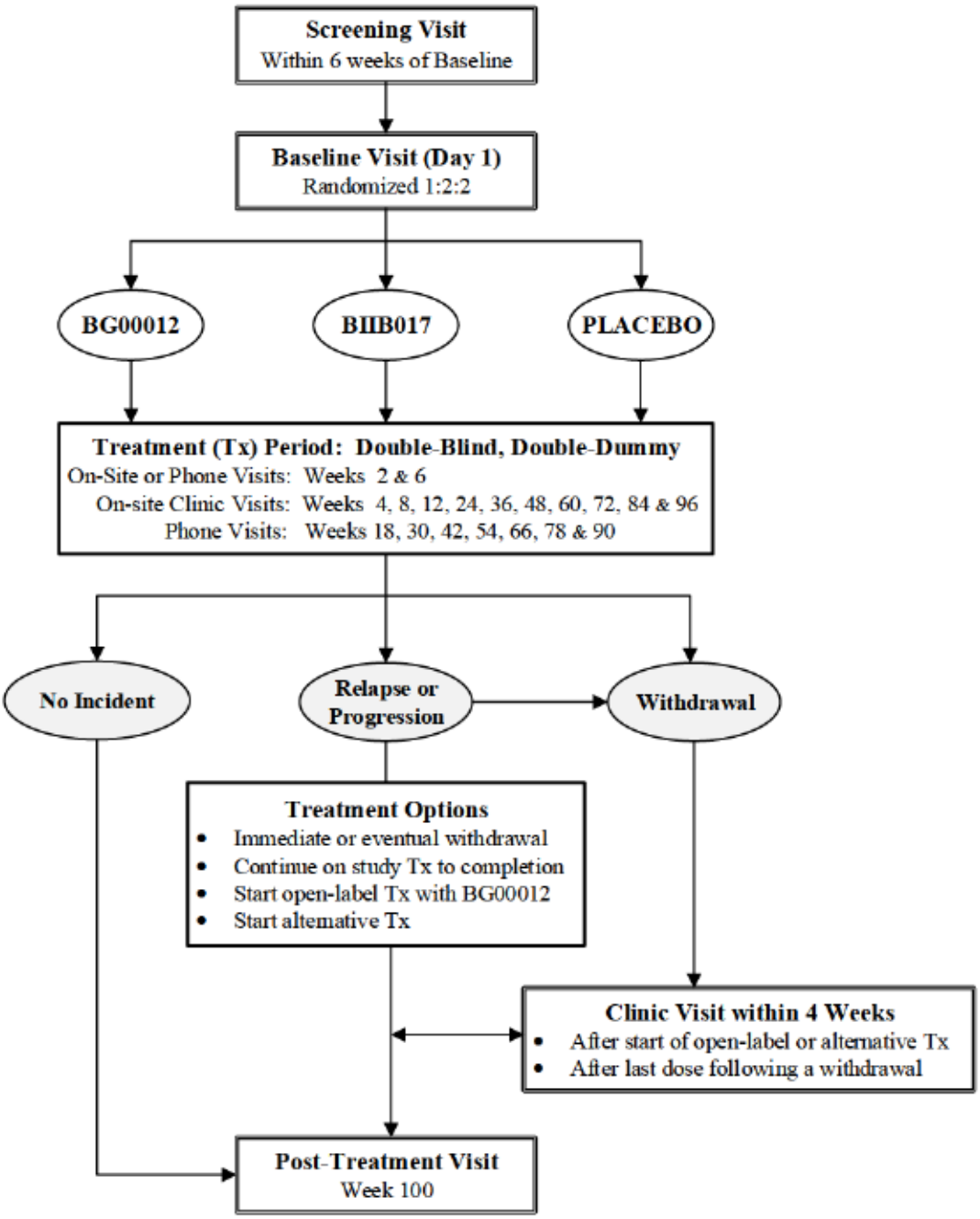
In addition to clinical monitoring for relapses, efficacy evaluations included assessments of brain MRIs with Gd enhancement at Baseline and Weeks 48 and 96; [redacted]. Safety was evaluated by the occurrence of AEs and SAEs as well as changes in [redacted].

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

Subjects whose lymphocyte count decreased to less than the lower limit of normal (LLN) while on study treatment were followed at least every 4 weeks until the lymphocyte count reached LLN. Subjects who completed, temporarily withheld, or permanently discontinued study treatment for any reason and had a lymphocyte count <LLN were to 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 was at least LLN, or for 48 weeks following treatment discontinuation, whichever occurred sooner, or until the subject was initiated on the appropriate MS treatment, according to local standard of care, following study withdrawal/completion.

See [redacted] below for a schematic of the study design.

Figure 1: Study Design



2.3. Sample Size Considerations

The primary endpoint of this study was 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 PARADIGMS study for fingolimod vs. Interferon β-1a (Chitnis, et al., 2018), and consistent with the understanding of pediatric MS, a higher relapse rate was observed in pediatric patients compared to adults. This is supported by internal Biogen Tecfidera trial data on younger adult patients. Based on the proportion of subjects relapsed (61.2%) in the Interferon β-1a arm, and the observed efficacy in DEFINE, CONFIRM (NCT00420212, studies 109MS301 and 109MS302), and PLEGRIDY (NCT00906399, ADVANCE study 105MS301), we conservatively assumed that 75% of subjects in the placebo group would have had their first relapse during the 2-year period. The study would have had 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) were expected to be accrued. The type I error of each comparison was controlled at 0.05. This 3-arm study was to 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 have been achieved in 2 separate placebo-controlled studies. However, the 3-arm platform design would allow 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 two separate studies, multiplicity adjustment were unnecessary. Taking into the account a 2-year discontinuation rate of 15%, the study planned 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 was monitored throughout the study, and discontinued subjects were planned to be replaced by new subjects to achieve 80% power.

2.4. Study stopping rules

The study protocol allowed Biogen to terminate the study at any time, after informing the Investigators. Biogen was required to notify the Investigators when the study status was changed, including study holds, study completion, and study termination.

3. Early termination of study due to sponsor's decision

The BLAST study was put on hold in 2021 due to low recruitment. After notification of all interested parties (investigators, IRBs, ethics committees, and regulatory agencies), BLAST was canceled by Biogen with the consent of the FDA. At the time the study was put on hold, 16 subjects had been screened and 11 subjects had been enrolled.

4. Changes from the protocol-defined statistical analysis plan

Due to the limited number of subjects enrolled and early closure of the study, the data obtained from this study are not sufficient to support the original study objectives and the analyses outlined in the protocol. The protocol statistical analysis plan was adjusted as reflected in this document to summarize the baseline characteristics and safety data. Summary tables of the baseline disease and demographic characteristics will be provided by treatment group; adverse events, [redacted] also will be descriptively evaluated: summaries by actual treatment received will be tabulated, with listing provided instead when the data are

limited. Drug efficacy and patient-reported outcome (PRO) data will not be summarized but will be provided in listings.

5. Definitions

Baseline Value: the last non-missing observation prior to receiving study treatment on or before Study Day 1.

[redacted]

Enrollment: Subjects will be enrolled in the study on the date the ICF is signed by the subject's legally authorized representative (LAR).

[redacted]

Relapse: A relapse is 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. If a subject experiences new neurologic symptoms, the subject (or parent) must contact the treating nurse or physician as soon as possible within 48 hours of the onset of symptoms. An AE should be recorded.

Study Day: Study Day 1 is the day of the first dose of study treatment. (It is the Baseline Day in most circumstances. If a necessary measurement is missing on Study Day 1, the baseline value is the last non-missing observation prior to receiving the study treatment on Study Day 1.)

For dates after Study Day 1

Study Day = (Date of assessment) – (Date of Study Day 1) + 1.

For dates prior to Study Day 1

Study Day = (Date of Assessment) – (Date of Study Day 1).

For adverse events

Onset Study Day = (Date of AE or worsening AE) – (Date of Study Day 1) + 1

For Time on Study

Study Duration = (End of Study Date) – (Date of Study Day 1) + 1

For Time on Treatment

Treatment Duration = (Date of last dose per CRF) – (Date of Study Day 1) + 1.

[redacted]

Treatment Emergent:

A treatment emergent AE is defined as any AE that either occurs or worsens in severity after the first dose of study treatment. If treatment emergence cannot be determined due to incomplete or partial start and/or end dates, the event will be considered treatment emergent.

5.1. Dates and Points of Reference

Assessment	Endpoint(s)	Study Visit	Target Day (Visit Window)
AE, SAE monitoring	Safety	Continuous from enrollment	N/A
[redacted]			

Assessment	Endpoint(s)	Study Visit	Target Day (Visit Window)
[redacted]			
Brain MRI ± Gd contrast agent.	Secondary Efficacy	Baseline Week 48 Week 96	Study Day 1 (1- 1) Day 337 (330- 344) Day 673 (666- 680)
Concomitant Medication Monitoring	Safety	Continuous from enrollment.	N/A
[redacted]			

Assessment	Endpoint(s)	Study Visit	Target Day (Visit Window)
[redacted]			

Assessment	Endpoint(s)	Study Visit	Target Day (Visit Window)
[redacted]			
[redacted]			

Assessment	Endpoint(s)	Study Visit	Target Day (Visit Window)
[redacted]			

5.2. Study Treatment

This study was a double-blinded, double-dummy, placebo-controlled trial. To maintain the blind all subjects received a placebo for the treatment they are not assigned.

BG00012 (Tecfidera) was to be taken orally at a dose of 120 mg BID for the first 7 days (1 capsule daily), and at 240 mg BID thereafter (2 capsules daily). The BG00012 treatment group will receive a placebo injection of BIIB017 vehicle every two weeks.

BIIB017 (Plegridy) was to be administered SC at a dose of 125 µg every two weeks for 96 weeks. BIIB012 subjects will be titrated to the target dose on the following schedule: 63 µg BIIB017 on Day 1, 94 µg at Week 2, and 125 µg every other week thereafter for the duration of the trial. BIIB017 subjects will receive daily placebo capsule(s) on the same schedule as BG00012 subjects.

Placebo subjects were to receive a SC injection of the BIIB017 vehicle every 2 weeks and daily placebo capsules according to the titration regimen for the BG00012 group.

5.3. Study Periods

This is a single period study, with no follow-up period. Screening took place up to 6 weeks prior to Study Day 1. Subjects were enrolled in the study after the informed consent was signed by their LAR.

5.4. Stratification Factors and Subgroup Variables

5.4.1. Stratification Factors

The study was stratified on age and site. Age was the subject age at Baseline (Study Day 1).

- Age
  - Baseline age 10 to less than or equal to 14 years
  - Baseline age greater than 14 years.
- Site—approximately 50 sites will be used world-wide.

Recruitment was used to ensure that at least 25% of subjects were in the 10 to less than or equal to 14 years age group. All analyses that fit a statistical model were to include the age stratification. Analyses were not to be stratified by site.

5.4.2. Subgroup Variables

No subgroup analyses are planned for this study.

5.5. Analysis Populations

The protocol defines two analysis populations.

Safety Population

The Safety population is defined as all subjects who received at least 1 dose of study treatment. Subjects will be analyzed according to the treatment received.

The primary safety analysis of AEs, [redacted] will be performed on the safety population during the period from the first dose of blinded treatment to the end of blinded treatment.

ITT Population

The Intent-to-Treat (ITT) Population is defined as all subjects 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.

6. List of Planned Study Analyses

As noted above, BLAST was terminated early due to the severely limited subject enrollment and progress in the study. As a result, the data collected are insufficient to support the original study objectives. The protocol study plan is changed as reflected in this document to briefly summarize the baseline characteristics and safety data by treatment group and overall. The data summaries are descriptive in nature: comparison among the study treatment groups is inappropriate. Drug efficacy and PRO data will not be summarized but will be provided in listings.

6.1. Interim Analysis

No interim analysis was planned for this study.

6.2. Primary Analysis

The primary analysis will be performed after the data base is locked. The primary analysis will consist of two parts: Subject summaries and Safety Analysis. The Subject summaries will provide a complete listing of all collected data for each subject. The Safety Analysis will consist of AE summaries, [redacted].

6.3. Final Analysis

The primary analysis is the final planned analysis. The BLAST study does not envision any long-term follow-up of subjects: the database will be complete at lock following the site close-out visits.

7. Statistical Methods for Planned Analyses

7.1. General Principles

The only planned analysis for this study is the final report. This study design is structured to minimize subject exposure to placebo, and because each active arm functions as a distinct study, multiplicity adjustments are unnecessary.

This is a double-blind, double-dummy study. The blind may be broken in case of a medical emergency if the treating physician needs to know the assigned treatment. Once unblinded, the subject will no longer receive study treatment. The investigator must document the cause for the unblinding in the source documents and make efforts to avoid unblinding other study personnel, limiting treatment information to those involved in the medical emergency.

Subjects will be instructed not to take a dose of study drug within 4 hours of a clinic visit to prevent drug-induced symptoms from being observed by study personnel and risk their unblinding. After the final clinical study report is completed, Biogen will inform the clinical investigators who may inform subjects about the treatment they received, if this does not jeopardize ongoing related studies.

Otherwise, all blinding will remain in place until the data base is locked.

Summary statistics for quantitative variables will consist of the mean, standard deviation, number of non-missing observations, minimum, the median, and the maximum. All quantitative data will be summarized with these statistics classified by treatment arm and visit unless otherwise noted below. Summary statistics for categorical data will consist of the frequency count and the percentage with respect to a study-relevant base (usually the number of subjects at-risk).

Among the demographic data, age, baseline height, and baseline weight will be summarized as quantitative variables. Race, ethnicity, sex, and [redacted] will be summarized as categorical variables. No graphics are planned for the demographic data.

Missing dates will be handled as shown in Table 1 below.

Table 1. Date imputation rules for AE and Concomitant Medication.

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

For all other situations if date imputation is appropriate the imputation rules are:

If the day is missing, default to the 15th of the month.

If month and day are missing, default to July 1 of the year.

If the year is missing, do not impute a date.

For all historical dates, if the imputation method yields a date after Study Day 1, impute Study Day – 2.

All analyses will be programmed in SAS® Version 9.4 or later.

7.2. Participant Accountability

The number of subjects enrolled, the number randomized who received at least one dose of study drug, the number discontinuing prior to Week 96 and the reason for withdrawal will be summarized by treatment assigned and overall.

A detailed listing of subject status, including screen failures will be created. This listing will show informed consent date, final study status, Study Day 1, and completion or withdrawal date, and for withdrawals, the reason for withdrawal. For screen failures, the primary reason for screen failure will be shown.

7.3. Demographic and Baseline Characteristics

The Safety Analysis Set's demographic characteristics will summarize age (in years, truncated to the year of age at baseline) as a quantitative variable by treatment arm and overall, and as counts and percent by treatment arm and overall, for the following categories: 10 to < 14, and 14 to <18 years.

Sex will be summarized as counts and percent for each treatment arm and overall.

Ethnicity (Latino/Not Latino/Not reported due to confidentiality regulations) will be summarized as counts and percent for each treatment arm and overall.

Race will be summarized by counts and percentage into American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Not reported due to confidentiality regulations, and Other. Other values will be listed but not further categorized. Baseline height (cm) and weight (kg) will be presented with summary statistics by treatment group and overall.

Summaries of baseline disease characteristics (MS disease history, e.g., time since the first MS symptom, time since MS diagnosis, the number of relapses in the past 12 mon, 2 years, the timing of the last relapse prior to enrollment and the [redacted]) will be presented by treatment group for the ITT Population. Medical history and MS Treatment history will be also summarized.

7.4. Protocol Deviations

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

7.5. Study Treatment Exposure and Concomitant Medications

Duration of study treatment and time on study will be summarized by treatment received for the Safety Population. Compliance until the last dose will also be summarized by treatment received for the Safety Population.

The number of doses taken will be computed per visit as

$$\text{Doses taken} = \text{Doses dispensed} - \text{Doses returned}.$$

The number of doses taken will be listed by visit. Compliance will be computed per subject as

Compliance = (Doses Taken – Doses Expected)/Doses Expected.

See Section 5 for the definitions of treatment duration and time on study.

A Concomitant therapy was defined as any therapy that was taken on or after the day of the first dose of study drug. This includes therapies that start prior to the initiation of the first dosing if their use continues on or after the date of the first dose. All concomitant medications were coded using the World Health Organization (WHO) medication dictionary (September 2021). All concomitant non-drug therapies were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) Version 24.1.

Numbers and percentages of subjects taking concomitant medications and non-drug therapies will be summarized by treatment group.

Efficacy Endpoints

All efficacy data will be listed for the ITT Population by treatment group and, for each subject, by visit and/or date. No statistical summaries will be provided. Listings will be provided for:

- Relapse data
- MRI parameters (the number of new or newly enlarging T2 hyperintense lesions compared to the prior visit, total number of Gd-enhancing lesions, [redacted], and [redacted])
- [redacted]
- [redacted]
- [redacted]

7.5.1. Primary Efficacy Endpoint

Because the number of subjects is limited, no analyses of the TTFR will be provided.

7.5.2. Secondary Efficacy Endpoints

Because the number of subjects is limited, no analyses of the secondary efficacy endpoints will be provided.

[redacted]

7.6. Safety Endpoints

7.6.1 Adverse Events

All treatment-emergent AEs will be included in the evaluation of safety. AEs were coded using the MedDRA version 24.1. The incidence of treatment-emergent AE and SAE will be summarized by system organ class (SOC) and preferred term (PT) for each treatment

and overall. An overall summary of AE will be created. The overall AE summary will include the incidence of the following treatment-emergent AEs:

- Number of subjects with an event
- Number of subjects with a moderate or severe event
- Number of subjects with a severe event
- Number of subjects with a related event
- Number of subjects with a serious event
- Number of subjects who discontinued study treatment due to an event
- Number of subjects who withdrew from the study due to an event

All AEs will be listed, including their treatment emergent status. AEs and SAEs will be classified by severity (mild, moderate, or severe) and relatedness (related or not related) to treatment by the investigator and included in the listing of all AEs. This listing will also include flags showing AEs that resulted in discontinuation of the study drug, AEs that resulted in withdrawal from the study, serious AEs, and AEs that led to dose reduction or interruption. In addition, a listing of deaths (blank page if none) will be provided.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.7. Pharmacokinetic (PK) Endpoints

N/A

7.8. Pharmacodynamic (PD) Endpoints

N/A

[redacted]

[redacted]

7.10. Antigenicity/Immunogenicity Endpoints

Immunogenicity data will be listed for the Safety Population by treatment received and, for each patient, by visit.

7.11. Other Analyses

N/A

7.12. Statistical Considerations for Interim Analysis

N/A

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

N/A

9. References

Chitnis, T., Arnold, D., Banwell, B., Bruck, W., Ghezzi, A., Giovannoni, G., . . . Wolinsky, J. (2018). Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis. *New England Journal of Medicine*, 379:1017-1027.

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

Polman CH, R. S. (2011). Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Ann Neurol.* , 69(2):292-302.

APPENDICES

Appendix A: Schedule of Activities (from Protocol 800MS301)

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															

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**
Urine Pregnancy Test[10,11]		X		X		X	X	X	X	X	X	X	X	X		X
[redacted]																
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]

[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]

[13] 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.

Appendix B: Schedule of Activities for 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; ECG = electrocardiogram; [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 Protocol 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.

[9]Urine cytology must be performed if microscopic hematuria of unknown etiology is present at the Early Withdrawal Visit.

[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]