STATISTICAL ANALYSIS PLAN

Version No.: 2.0

Date: 31 July 2020

Author: [redacted]

Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with Optional Open-Label Extension in Subjects With Relapsing Multiple Sclerosis to Evaluate the Efficacy and Safety of BIIB033 as an Add-On Therapy to Anti-Inflammatory Disease-Modifying Therapies

Name of Study Treatment: BIIB033

Protocol No.: 215MS202/NCT03222973

Study Phase: Phase II

APPROVAL

This document has been reviewed and approved by:		
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RDPT Statistician	S	Date
[redacted]	DocuSigned by: [redacted]	10-Aug-2020
Study Medical Lead		Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
Draft version 1.0	03-August-2018	Draft version.
Stable version 1.0	28-September-2018	Stable version.
Final version 1.0	01-September-2019	Finalized version 1.
Final version 2.0	31-July-2020	Finalized version 2. to use new SAP template and some amendment to planned analyses including additional supportive endpoints for clinical disability measures.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
[redacted]	[redacted]
9HPT-D, ND	9-Hole Peg Test (dominant hand, nondominant hand)
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamate pyruvate transaminase
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
CBH	chronic black holes
CDI	confirmed disability improvement
CDW	confirmed disability worsening
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	data monitoring committee
DMF	dimethyl fumarate
DMT	disease-modifying therapy
DNA	deoxyribonucleic acid
[redacted]	[redacted]
[redacted]	[redacted] – [redacted]
[redacted]	[redacted] – [redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
EMS	Early Multiple Sclerosis
EOS	End of Study
ET	Early Termination
FSH	Follicle-stimulating hormone
GA	glatiramer acetate
GCP	Good Clinical Practice
[redacted]	[redacted]
GGT	Gamma glutamyl transferase
ICF	Informed Consent Form
IFN-β	interferon beta
ITT	intent-to-treat
IV	intravenous
IRT	Item Response Theory
[redacted]	[redacted]
mAb	monoclonal antibody
MCE	multicomponent endpoint
MMRM	Mixed Model for Repeated Measures
[redacted]	[redacted]
MS	multiple sclerosis
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ORS	Overall Response Score
PASAT-3	3-Second Paced Auditory Serial Addition Test
[redacted]	
PK	pharmacokinetics
[redacted]	
PT	Prothrombin time
PTT	Partial thromboplastin time
RMS	relapsing multiple sclerosis
[redacted]	[redacted]
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	Statistical analysis plan
SD	standard deviation
SDMT	Symbol-Digit Modalities Test
SPMS	secondary progressive multiple sclerosis
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
T25FW	Timed 25-Foot Walk
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. Introduction

The purpose of this SAP is to delineate the statistical analyses as outlined in the 215MS202 Protocol V3, with details focusing on the study primary analysis, i.e., the Study Part 1 analysis.

2. Study Overview

2.1. Study Objectives and Endpoints

2.1.1. Primary Objective

The primary objective of the study is to evaluate the effects of BIIB033 versus placebo on disability improvement over 72 weeks.

2.1.2. Primary Endpoint

The primary endpoint is the Overall Response Score (ORS), assessed over 72 weeks of the study.

The ORS is a multicomponent score based on 4 components: EDSS, T25FW, 9HPT-D, and 9HPT-ND. It assesses overall changes in disability over time.

At each visit, each assessment is given a score compared to baseline. Meeting or exceeding the threshold for improvement in an assessment results in a +1 score for that assessment; meeting or exceeding the threshold for worsening in an assessment results in a -1 score for that assessment; no change or subthreshold changes in an assessment results in a score of 0 for that assessment. The scores of individual assessments are summed up to provide a total ORS that ranges from +4 to -4 for each visit.

2.1.3. Secondary Objective

The secondary objective of this study is to evaluate the effects of BIIB033 versus placebo on additional measures of disability improvement.

2.1.4. Secondary Endpoints

The secondary endpoints are as follows:

- Proportion of subjects with 12-week confirmed improvement (CDI) in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D and 9HPT-ND.
- Proportion of subjects with 12-week CDI in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND and PASAT-3.
- Proportion of subjects with 12-week CDI in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and without confirmed disability worsening in any of the 4 assessments during the 72 weeks of the study.
- Proportion of subjects with 12-week CDI in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND and SDMT.
- Proportion of subjects with 12-week CDI in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D and 9HPT-ND (20% thresholds for T25FW and 9HPT).

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2.2. Study Design

This is a Phase 2 multicenter study conducted in 2 parts. Part 1 is a 72-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 study to evaluate the efficacy and safety of BIIB033 (750 mg infused IV every 4 weeks) as an add-on therapy to a

background DMT in subjects with RMS. Part 2 is a 96-week open-label extension that will assess long-term safety and efficacy of BIIB033 administered for approximately 24 additional months.

In Part 1 of the study, approximately 240 eligible subjects will be randomized into the active treatment group (BIIB033 750 mg) or placebo in a 1:1 ratio at approximately 150 sites in approximately 25 countries. Randomization will be stratified by MS type (RRMS versus SPMS), background DMT group, [redacted].

The study treatment in Part 1 includes BIIB033 or placebo, administered once every 4 weeks by IV infusion for a total of 19 doses over 72 weeks. All enrolled subjects must have been treated for at least 24 consecutive weeks prior to enrollment on an anti-inflammatory DMT and will continue taking their DMT throughout the study. Based on the clinical judgment of the treating neurologist, subjects can switch to another marketed DMT during the study or may discontinue the DMT altogether.

Each subject in Part 1 will have a total of 21 scheduled study visits:

- Screening (pre-treatment)
- Treatment Period: 1 visit every 4 weeks between Day 1/Baseline and Week 72 (19 visits)
- Follow-up Period (Post-treatment): End of Study (EOS) Visit (Week 84) for subjects who do not participate in Part 2.

Part 1 of the study will include clinical assessments every 12 weeks. Each subject will have separate treating and examining neurologists; the roles of the treating and examining neurologist are not interchangeable even for different subjects.

In Part 2 of the study, subjects who have completed study treatment (BIIB033 or placebo) in Part 1, have consented and are eligible to participate in Part 2 of the study will be enrolled.

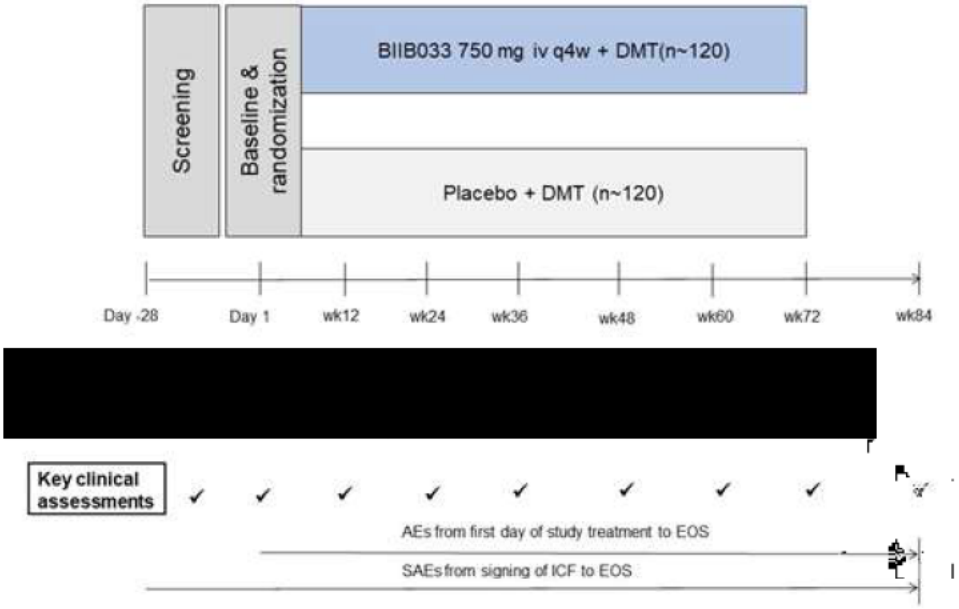
Subjects enrolled in Part 2 of the study will receive BIIB033 by IV infusion once every 4 weeks for a period of approximately 96 weeks. All subjects in Part 2 will continue the anti-inflammatory DMT used at the end of Part 1. The maximum allowed time for rollover into Part 2 of the study (Day 1) is 12 weeks after the Part 1/Week 72 Visit. Clinic visits will be conducted once every 24 weeks, [redacted].

[redacted]

Study treatment allocation in Part 1 will remain blinded for all Part 2 subjects and all site staff.

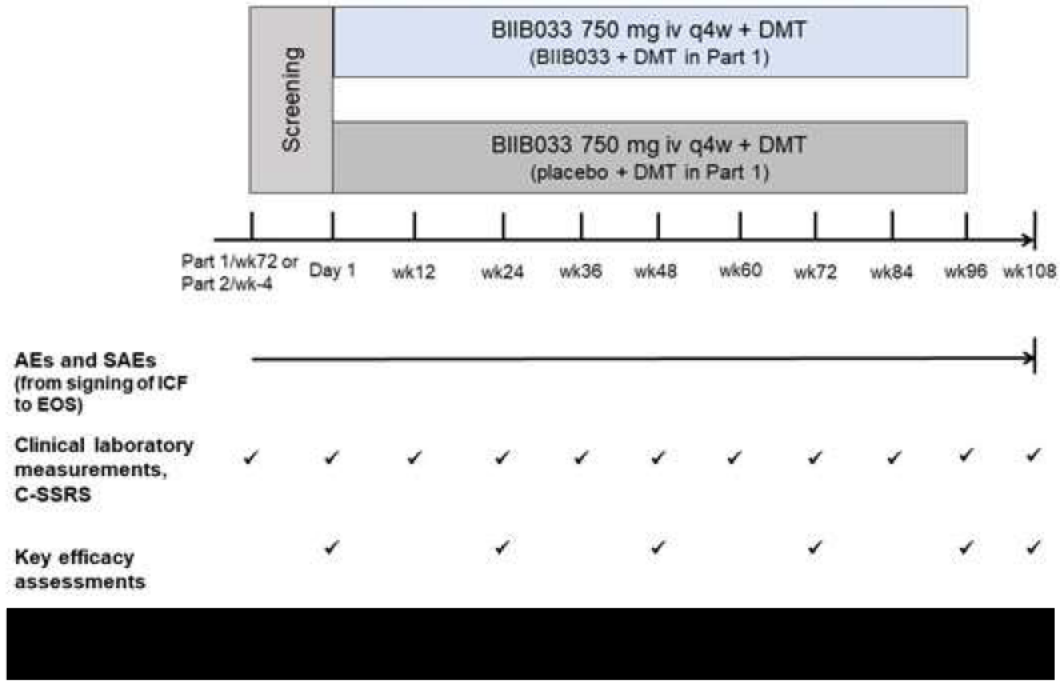
See **Figure 1** and **Figure 2** for a schematic of the study design for Part 1 and Part 2, respectively.

Figure 1: Part 1- Study Schematic



AE = adverse event; DMT=disease-modifying therapy; EOS = End of Study; ICF = informed consent form; IV=intravenous; [redacted]; n=number of patients; q4w=every 4 weeks; SAE = serious adverse event; wk = week

Figure 2: Part 2 – Study Schematic



AE = adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; DMT=disease-modifying therapy; EOS = End of Study; ICF = informed consent form; IV=intravenous; [redacted]; n=number of patients; q4w=every 4 weeks; SAE = serious adverse event; wk = week

2.3. Study Duration for Subjects

The total duration of study participation in Part 1 for each subject will be up to approximately 88 weeks; this consists of a Screening Period of up to 4 weeks, a Treatment Period of 72 weeks, and a Follow-up Period of 12 weeks. Subjects enrolled in Part 2 do not need to have the 12-week follow-up (EOS) after the last dose of study treatment in Part 1; thus, the study duration in Part 1 will be approximately 76 weeks.

The total duration of study participation in Part 2 for each subject will be up to approximately 112 weeks; this consists of a Screening Period of up to 4 weeks, a Treatment Period of 96 weeks, and a Follow-up Period of 12 weeks.

The total duration for subjects who participate in both Part 1 and Part 2 will be approximately 188 weeks.

For details about Screening, Treatment Period, unscheduled visits(s) and treatment for relapse and Follow-up, please see protocol Section 7.2.

2.4. Sample Size Considerations

In Part 1, a sample size of 120 subjects per treatment group will have approximately 80% power to detect a treatment effect of 0.354 in ORS over 72 weeks comparing to placebo. This power calculation is based on a 1-sided 2-sample t-test assuming equal variance with a significance level of 0.025, an SD of 0.85, and a drop-out rate of 20%. The assumed treatment effect of 0.354 is based on the 90% one-sided lower confidence bound of the estimated treatment effect in the target population of Study 215MS201.

3. Definitions

3.1. Study Treatment

Study treatment in this SAP, unless otherwise specified, refers to the blinded treatment in Part 1 of either BIIB033 750 mg or placebo, administered once every 4 weeks (Q4W) by intravenous (IV) infusion for the planned a total of 19 doses over 72 weeks, added on to anti-inflammatory DMT. Throughout this SAP, study treatment and *study drug* are equivalent and used interchangeably.

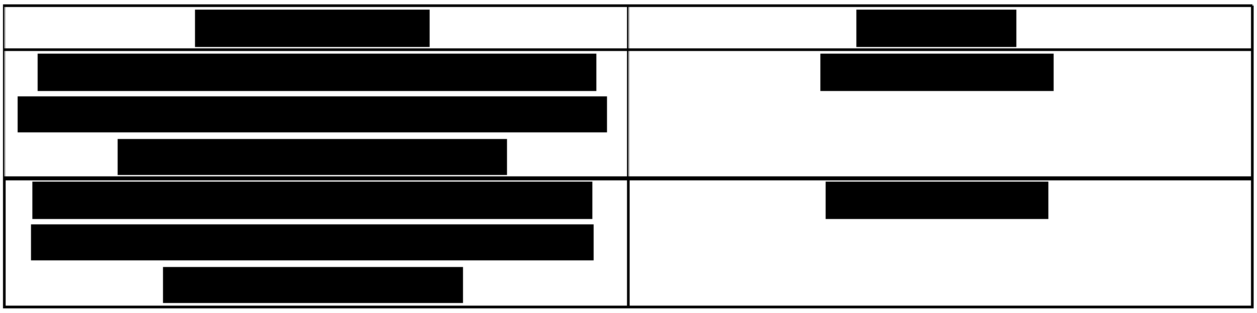
To facilitate illustration in the analysis plan, treatment groups are listed below with short names:

Table 1: Treatment Groups

Part 1 Analyses (Interim Analysis, Primary Analysis):

Study Treatment	Short name
Blinded BIIB033 750 mg IV infusion Q4W	BIIB033
Blinded Placebo IV infusion Q4W	Placebo

[redacted]



3.2. Dates and Points of Reference

Study Day 1

The *study Day 1* is defined as the date on which the first dose of study treatment is administered in Part 1.

First Dose Date and Last Dose Date

Without otherwise specified, the *first dose date* is equivalent to study Day 1 defined above, the *last dose date* is the date of the last administration of study treatment in Part 1.

End of Treatment (EOT) / Early Termination (ET)

In the event that a subject withdraws from the study prematurely, an ET visit should be performed as soon as possible but no later than 4 weeks after the last dose of study treatment. The End of Treatment eCRF page should be filled out at the ET visit. The *EOT date* is the End of Treatment – PART 1 date recorded on the End of Treatment eCRF page. The *ET visit date* refers to the date of visit for the ET visit.

End of Study (EOS)

For subjects who complete Part 1 and do not enroll into Part 2, the EOS visit is defined as the Week 84 visit; for subjects who early terminate in Part 1, the EOS visit is defined as the scheduled follow-up visit after the ET visit, this EOS visit is to occur approximately 12 weeks after the last dose of study treatment in Part 1; for subjects who complete Part 1 and are enrolled into Part 2, the EOS visit is to occur approximately 12 weeks after the last dose of study treatment in Part 2. *The EOS date* is the End of Study date recorded on the End of Study eCRF page. The last date in Part 1 is the latest date among all visits' end dates if a subject does not have Part 2 Day 1 visit; the last date in Part 1 is the day prior to the start date of Part 2 Day 1 visit if a subject has Part 2 Day 1 visit.

DMT Switch Date

During the study period, subjects will take the same protocol-specified DMT they have been treated with for at least 24 weeks prior to study Day 1. This is referred to as background DMT (Section 3.5.1). But based on the clinical judgment of the treating neurologist, subjects can switch to another marketed DMT or may discontinue the DMT altogether. Subjects who switch DMT will be identified from the DMT Treatment eCRF page. For a subject who switches DMT, the *DMT switch date* is when the subject starts the first dose of the new DMT.

Start Date of COVID-19 Phase

COVID-19 phase refers to the time period during which conduct of this study is impacted by COVID-19 infection or COVID-19 pandemic measures. The start date of the COVID-19 phase for this study is March 15, 2020.

COVID-19 Pandemic Measures

Refer to any action or challenges arising due to COVID-19 that may impact study conduct, including quarantines, site closures, travel limitation, interruptions to the supply chain for the investigational product, or other considerations if site personnel become infected with COVID-19.

Study Day

- For a date on or after Study Day 1

  Study Day = (Date of Interest) – (Study Day 1) + 1

- For a date before Study Day 1

  Study Day = (Date of Interest) – (Study Day 1)

Visit Window Mapping

For data that are summarized by visit and longitudinal analysis, assessment from all scheduled visits including ET visits and EOS visits, and all unscheduled visits in Part 1 will be mapped to an appropriate analysis visit using a windowing scheme. The analysis visit windows are defined in **Table 5** for different endpoints. To define the analysis visit window, the target visit day is calculated as (week number×7+1). The lower bound of the visit window is calculated as (target visit day + (target visit day of the previous visit))/2+1, except for the first post-baseline visit window whose lower bound is set as Day 2; the upper bound of the visit window is calculated as (target visit day + (target visit day of the next visit))/2; the upper bound of the last visit in Part 1 is the date of the EOS/ET visit in Part 1 for subjects who are not enrolled in Part 2, or (Part 2 Day 1) – 1 for those who are enrolled in Part 2 of the study.

If more than one assessment is within the same analysis visit window other than ET or EOS visits, the assessment closest to the target visit day will be used for the analysis. If more than one assessment falls in the same distance from the target visit day other than ET or EOS visits, the last one will be used for the analysis. If more than one assessment is on the same day other than ET or EOS visits, the average value for the quantitative parameters and the worst value for the qualitative parameters will be used for the analysis.

If the ET visit is mapped to the same analysis visit as a prior visit (either scheduled or unscheduled visit), then the ET visit will be remapped to the next analysis visit. If EOS visit is mapped to an analysis visit and a prior visit, e.g. ET visit, is mapped to the same analysis visit, then EOS visit will be remapped to the next analysis visit. The latest analysis visit for the ET visit can be up to Week 72 and for the EOS visit can be up to Week 84.

As Part 2 Screening visit should be performed as part of Part 1 Week 72 visit but a separate Part 2 Screening visit is allowed, for subjects who have screening for Part 2 but do not rollover to Part 2, they may not have a separate Part 2 Screening visit or may have Part 2 Screening visit as a separate visit after Week 72 visit; for subjects who have screening for Part 2 and rollover to Part 2, they will have Part 2 Day 1 visit, in addition, they may not have a separate Part 2

Screening visit or may have Part 2 Screening visit as a separate visit after Week 72 visit. We do not map Part 2 screening visit and Part 2 Day 1 visit.

3.3. Study Periods

Study Baseline Period and Baseline Data

The study baseline period is defined as the period from screening visit to the day prior to first administration of study treatment.

Unless stated otherwise, study *baseline data* are defined as the data collected prior to the first dose, which is usually at the Day 1/Baseline visit. If there is more than one value on or before the first dose, the non-missing value closest to and prior to the first dose will be used as the baseline value.

Actual Treatment Period in Study Part 1

Actual treatment period in Part 1 of the study is defined as the period from the first infusion of study treatment to 28 days after the last infusion of study treatment in Part 1.

Treatment Emergent

An adverse event in Part 1 is defined as the event that has onset date/time prior to Part 2 Day 1 infusion day. If a subject is not enrolled in Part 2 or is enrolled in Part 2 but never receives infusion of study treatment in Part 2, all adverse events will be considered as occurring in Part 1.

An adverse event is regarded as *treatment emergent in Part 1* of the study if the event has onset date/time on or after the first dose date/time of study treatment, or was reported prior to the first dose and subsequently worsens in severity after first dose date. Additional criteria to determine treatment emergent are described in Section 5.8.2. Unless otherwise specified, the phrase "treatment emergent" in this SAP refers to "treatment emergent in Part 1".

3.4. Key Derived Variables

3.4.1. Thresholds for Improvement and Worsening

The thresholds are defined as following:

- **Thresholds for EDSS**
    - Improvement is defined as a ≥ 1.0-point decrease in EDSS from a baseline score of ≤6.0.
    - Worsening is defined as a ≥1.0-point increase from a baseline score of ≤5.5 or a ≥0.5-point increase from a baseline score equal to 6.0
- **15% Thresholds for T25FW, 9HPT-D and 9HPT-ND**
    - Improvement is defined as ≥15% decrease from baseline in time (seconds)
    - Worsening is defined as ≥15% increase from baseline in time (seconds)

  Throughout this SAP document, unless otherwise specified, 15% is used as the threshold for T25FW, 9HPT-D, and 9HPT-ND.
- **20% Thresholds for T25FW, 9HPT-D and 9HPT-ND**

- Improvement is defined as ≥20% decrease from baseline in time (seconds)
- Worsening is defined as ≥20% increase from baseline in time (seconds)

The phrase "20% thresholds for T25FW and 9HPT" in the protocol and the SAP refers to the case that 20% being used as the threshold for T25FW, 9HPT-D, and 9HPT-ND.

- **Threshold for PASAT-3**
  - Improvement is defined as ≥15% decrease from baseline in score
- **Threshold for SDMT**
  - Improvement is defined as a ≥4-point increase from baseline
- [redacted]

3.4.2. Definitions of Confirmed Disability Improvement and Confirmed Disability Worsening

3.4.2.1. Confirmed Disability Improvement (CDI)

CDI is assessed for each of the efficacy components (EDSS, T25FW, 9HPT-D, 9HPT-ND, PASAT-3, SDMT, [redacted]) in the first place using the improvement threshold for each of the components defined in Section 3.4.1; then CDI in a multicomponent endpoint (MCE) is determined based on the CDI results of the components that constitute the MCE. Improvement in T25FW, 9HPT-D, 9HPT-ND and PASAT-3 will be derived after the imputation rules described in Section 5.2.1 are applied.

60-day Relapse Window

A *60-day relapse window* is employed for some conditions in the CDI and CDW derivations. A subject is regarded as having a relapse for at least 60 days after the onset of a protocol-defined relapse. At each (unscheduled) relapse visit, the investigator will evaluate whether the subject experiences a protocol-defined MS relapse. A visit is considered as within the 60-day relapse window if (date of the visit – onset date of the protocol-defined MS relapse) <60 days.

Potential Improvement and Tentative Improvement

For each component, a *potential improvement* is observed at a given visit if the improvement threshold is met at this visit but is not met at the previous visit, and no CDI has been identified up to this visit since study Day 1.

Assessment at any unscheduled visit will not be used for either potential improvement or improvement confirmation.

To be eligible for evaluation of CDI, potential improvement must start in the actual treatment period defined in Section 3.3. Visits outside of the actual treatment period can only be used to confirm potential improvements that start within the actual treatment period. If a potential improvement is observed in the actual treatment period but there is no later assessment in the remaining study period, then the improvement cannot be confirmed, and the potential

improvement in this case is termed as *tentative improvement*. Alternative approaches considering tentative improvement may be used as supportive analyses (Section 5.7.3.2).

Confirmed disability improvement will be assessed as follows.

12-week CDI

The *12-week confirmation visit* in default refers to the visit that should occur, per schedule of events (Appendix IV), 12 weeks after the visit with a potential improvement observed. If the default confirmation visit is missing, the next scheduled visit that actually occurs will be used as the 12-week confirmation visit.

For each component, a *12-week CDI* is identified if the improvement threshold for the same component is met again at the 12-week confirmation visit that is ≥74 days after the visit with the potential improvement. The 74 days is the minimum distance between 2 consecutive scheduled visits with a target distance of 84 days and a protocol allowed ±5-day visit window. In the event that the improvement at 12-week confirmation visit is <74 days apart from the potential improvement, or that the result at this visit fails to meet the improvement threshold but is assessed within a 60-day relapse window, the next scheduled visit subsequent to this 12-week confirmation visit can confirm the potential improvement if having an improvement observed.

The ET and EOS visits are treated as scheduled visits and the corresponding assessments can be used to confirm the potential improvement observed at the latest scheduled visit prior to ET or EOS regardless of the 74-day requirement. For example, if a subject has a potential improvement followed by an ET visit and an EOS visit, both with non-missing results, then the result at the ET visit will be used to confirm the potential improvement regardless of the number of days between the potential improvement and the ET visit.

24-week CDI

The *24-week confirmation visit* in default refers to the visit that should occur, per schedule of events (Appendix IV), 24 weeks after the visit with a potential improvement observed. If the default confirmation visit is missing, the next scheduled visit that actually occurs will be used as the 24-week confirmation visit.

For each component, a *24-week CDI* is identified if the improvement threshold for the same component is met at the 24-week confirmation visit, and is also met at any scheduled visit between the potential improvement and 24-week confirmation visit unless the scheduled visit in between is within a 60-day relapse window.

The improvement at 24-week confirmation visit is required to be ≥158 days apart from the potential improvement to be confirmed. The 158 days is the minimum distance between 2 scheduled visits with a target distance of 24 weeks (168 days) and a protocol allowed ±5-day visit window. In the event that the improvement at 24-week confirmation visit is <158 days apart from the potential improvement, or that the result at this visit fails to meet the improvement threshold but is assessed within a 60-day relapse window, the next scheduled visit subsequent to this 24-week confirmation visit can confirm the potential improvement if having an improvement observed.

The ET and EOS visits are treated as scheduled visits and the corresponding assessments can be used to confirm the potential improvement observed at the latest 2 scheduled visits (assessments are taken every 12 weeks per protocol schedule) prior to ET or EOS regardless of the 158-day requirement. For example, if a subject has a potential improvement followed by an ET visit and an EOS visit, both with non-missing results, then the result at the ET visit will be used to confirm the potential improvement regardless of the number of days between the potential improvement and the ET visit. In this case, CDI is identified if improvement threshold is met at the ET visit, as well as at the scheduled visit, if there is any, between the potential improvement and the ET visit.

CDI in an Individual Component

For a disability assessment (e.g., EDSS, T25FW) that may be used to constitute an MCE together with other disability assessments, if a subject has a potential improvement that is later confirmed following the criteria aforementioned in this section, then the subject is considered as *with CDI in this component*, and the potential improvement that gets later confirmed is assigned as the actual *CDI event of the component*.

Time to CDI in an Individual Component

For a given individual component, the time to CDI in this component is defined as the number of days from the study Day 1 to the date of the CDI event of this component as defined above. For subjects without CDI in this component, the time to CDI in this component is censored at the date of the subject's latest scheduled visit in the actual treatment period at which the result is non-missing, including the case that the subject is unable to complete this component assessment due to MS-related physical limitations. If a subject has missing value of the individual component at the Day 1/Baseline visit, for example, the subject has no assessment at Day 1, or the result of the assessment at Day 1 is not available due to any other reason, then the censoring date will be set as Day 1. Assessment at any unscheduled visit will not be used to determine the censoring time.

CDI in a Multicomponent Endpoint (MCE)

If a subject is with CDI in one or more components that constitute an MCE, then the subject is considered as *with CDI in this MCE*, and the first CDI event of any component is assigned as the actual *CDI event of the MCE*.

Time to CDI in an MCE

The time to CDI in an MCE is defined as the number of days from the study Day 1 to the date of the first CDI event of the MCE as defined above. For subjects without CDI in this MCE, the time to CDI in this MCE is censored at the latest date among the subject's censoring dates for each component constituting this MCE.

3.4.2.2. Confirmed Disability Worsening (CDW)

CDW is assessed for each of the efficacy components (EDSS, T25FW, 9HPT-D and 9HPT-ND) in the first place using the threshold for each of the components defined in Section 3.4.1; then CDW in an MCE is determined based on the CDW results of the components that constitute this MCE. Worsening in T25FW, 9HPT-D and 9HPT-ND will be derived after the imputation rules described in Section 5.2.1 are applied.

In any case, disability worsening cannot be confirmed if there is a recent relapse and the visit used for confirmation is within a 60-day relapse window as defined in Section 3.4.2.1.

Potential Worsening and Tentative Worsening

For each component, a *potential worsening* is observed at a given visit if worsening threshold is met at this visit but is not met at the previous visit, and no CDW has been identified up to this visit since study Day 1.

An unscheduled visit associated with a protocol-defined MS relapse can be used to identify potential worsening, but cannot be used to confirm a worsening itself. Instead, if following a potential worsening the worsening threshold is met again at this unscheduled relapse visit, then the next visit subsequent to this unscheduled relapse visit will be used for worsening confirmation.

To be eligible for evaluation of CDW, potential worsening must start in the actual treatment period defined in Section 3.3. Visits outside the actual treatment period can only be used to confirm potential worsening events that start within the actual treatment period. If a potential worsening is observed in the actual treatment period but there is no later assessment in the remaining study period, then the worsening cannot be confirmed, and the potential improvement in this case is termed as *tentative worsening*.

Confirmed disability worsening will be assessed as follows.

12-week CDW

The *12-week confirmation visit* in default refers to the visit that should occur, per schedule of events (Appendix IV), 12 weeks after the visit with a potential worsening observed. If the default confirmation visit is missing, the next scheduled visit or unscheduled relapse visit that actually occurs will be used as the 12-week confirmation visit.

For each component, a *12-week CDW* is identified if the worsening threshold for the same component is met again at the 12-week confirmation visit, which is ≥74 days after the visit with the potential worsening and not within a 60-day relapse window. In the event that the worsening at the 12-week confirmation visit is <74 days apart from the potential worsening or within a 60-day relapse window, the next visit subsequent to this 12-week confirmation visit can confirm the potential worsening if having a worsening observed and not within a 60-day relapse window.

The ET and EOS visits are treated as scheduled visits and the corresponding assessment can be used to confirm a previous potential worsening if there is no scheduled visit between the potential worsening and the ET or EOS regardless of the 74-day requirement. For example, if a subject has a potential worsening followed by an ET visit and an EOS visit, both with non-missing results and not within a 60-day relapse window, then the result at ET visit will be used to confirm the potential worsening regardless of the number of days between the potential worsening and the ET visit.

24-week CDW

The *24-week confirmation visit* in default refers to the visit that should occur, per schedule of events (Appendix IV), 24 weeks after the visit with a potential worsening observed. If the default

confirmation visit is missing, the next scheduled visit or unscheduled relapse visit that actually occurs will be used as the 24-week confirmation visit.

For each component, a *24-week CDW* is identified if the worsening threshold for the same component is met at the 24-week confirmation visit, and is also met at any scheduled visit between the potential worsening and the 24-week confirmation visit.

The worsening at the 24-week confirmation visit is required to be ≥158 days apart from the potential worsening to be confirmed. In the event that the worsening at 24-week confirmation visit is <158 days apart from the potential worsening or within a 60-day relapse window, the next visit subsequent to this 24-week confirmation visit can confirm the potential worsening if having a worsening observed and not within a 60-day relapse window.

The ET and EOS visits are treated as scheduled visits and the corresponding assessment can be used to confirm the potential worsening observed at the latest 2 scheduled visits (assessments are taken every 12 weeks per protocol schedule) prior to ET or EOS regardless of the 158-day requirement. For example, if a subject has a potential worsening followed by an ET visit and an EOS visit, both with non-missing results, then the result at the ET visit will be used to confirm the potential worsening regardless of the number of days between the potential worsening and the ET visit. In this case, CDW is identified if worsening threshold is met at the ET visit, as well as at any other visit, if there is any, between the potential worsening and the ET visit.

CDW in an Individual Component

For a disability assessment (e.g., EDSS, T25FW) that may be used to constitute an MCE together with other disability assessments, if a subject has a potential worsening that is later confirmed following the criteria aforementioned in this section, then the subject is considered as *with CDW in this component*, and the potential worsening that gets later confirmed is assigned as the actual *CDW event of the component*.

Time to CDW in an Individual Component

For a given individual component, the time to CDW in this component is defined as the number of days from the study Day 1 to the date of the CDW event of this component as defined above. For subjects without CDW in this component, the time to CDW in this component is censored at the date of the subject's latest visit (considering all scheduled visits and unscheduled visit where a protocol-defined MS relapse is asserted) in the actual treatment period at which the result is non-missing, including the case that the subject is unable to complete this component assessment due to MS-related physical limitations. If a subject has missing value of the individual component at the Day 1/Baseline visit, for example, the subject has no assessment at Day 1, or the result of the assessment at Day 1 is not available due to any other reason, then the censoring date will be set as Day 1.

CDW in an MCE

If a subject is with CDW in one or more components that constitute an MCE, then the subject is considered as *with CDW in this MCE*, and the first CDW event of any component is assigned as the actual *CDW event of the MCE*.

Time to CDW in an MCE

The time to CDW in an MCE is defined as the number of days from the study Day 1 to the date of the first CDW event of this MCE as defined above. For subjects without CDW in this MCE, the time to CDW in this MCE is censored at the latest date among the subject's censoring dates for each component constituting the MCE.

3.4.2.3. CDI Without Confirmed Disability Worsening

Unless otherwise specified, this refers to the 12-week CDI in at least 1 of the following 4 assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and without confirmed disability worsening in any of these 4 assessments during the 72 weeks of the study.

Essentially, this CDI without confirmed disability worsening defines a subset of subjects with CDI, with the condition further selecting subjects who are without CDW during the 72 weeks of the study. For the subset of subjects identified as having CDI without confirmed disability worsening, the assignment of the event and the time to event for this endpoint are the same as that of the assignment of CDI event and time to CDI as defined in Section 3.4.2.1. The rest of subjects are considered as not with this CDI without confirmed disability worsening. For such subjects the censoring date is the date of the subject's latest scheduled visit in the actual treatment period at which the result is non-missing, including the case that the subject is unable to complete this component assessment due to MS-related physical limitations.

3.4.2.4. CDW Without Confirmed Disability Improvement

Unless otherwise specified, this refers to the 12-week CDW in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and without confirmed disability improvement in any of the 4 assessments during the 72 weeks of the study.

Essentially, this CDW without confirmed disability improvement defines a subset of subjects with CDW, with the condition further selecting subjects who are without CDI during the 72 weeks of the study. For the subset of subjects identified as having CDW without confirmed disability improvement, the assignment of the event and the time to event for this endpoint are the same as that of the assignment of CDW event and time to CDW as defined in Section 3.4.2.2. The rest of subjects are considered as not with this CDW without confirmed disability improvement. For such subjects the censoring date is the date of the subject's latest visit (considering all scheduled visits and unscheduled visit where a protocol-defined MS relapse is asserted) in the actual treatment period at which the result is non-missing, including the case that the subject is unable to complete this component assessment due to MS-related physical limitations.

3.4.2.5. CDI in Two or More Components

A subject is considered with *CDI in two or more components* if the subject has 12-week CDI in two or more of the assessments during the 72 weeks of study: EDSS, T25FW and 9HPT either hand. The CDI in 9HPT is only counted as one assessment here. Specifically, subjects with CDI in two or more components include

- Subjects with 12-week CDI in EDSS and 12-week CDI in T25FW
- Subjects with 12-week CDI in EDSS and 12-week CDI in 9HPT either hand (12-week CDI in 9HPT-D or 12-week CDI in 9HPT-ND)

- Subjects with 12-week CDI in T25FW and 12-week CDI in 9HPT either hand (12-week CDI in 9HPT-D or 12-week CDI in 9HPT-ND)
- Subjects with 12-week CDI in EDSS, 12-week CDI in T25FW and 12-week CDI in 9HPT either hand (12-week CDI in 9HPT-D or 12-week CDI in 9HPT-ND)

Again, there are three components considered here: EDSS, T25FW and 9HPT either hand. The time to CDI in EDSS or T25FW follows the time to CDI in individual component defined in Section 3.4.2.1. For 9HPT either hand, if a subject has CDI in both hands, then the hand with the earlier CDI is used to set the time to CDI in 9HPT either hand.

For subjects with the event of CDI in two or more components, the time to event is calculated as the number of days between the first dose date and the second CDI date of the two or more individual components that achieve CDI:

- The date of CDI in EDSS
- The date of CDI in T25FW
- The date of CDI in 9HPT (based on the hand with the earlier CDI date if CDI is achieved in both hands)

For example, if a subject has a CDI in both EDSS and T25FW, and thus this subject has a CDI in two or more components. Suppose time to CDI in EDSS is 84 days, and the time to CDI in T25FW is 112 days, then the time to confirmed improvement is 112 days.

For a subject who does not have CDI in two or more components, the time to this endpoint is censored at the latest date among the subject's censoring dates for each component (EDSS, T25FW, 9HPT-D and 9HPT-ND). Here the date of CDI and censoring date of CDI in individual component all follow Section 3.4.2.1.

3.4.2.6. CDI Excluding Data after DMT Switch

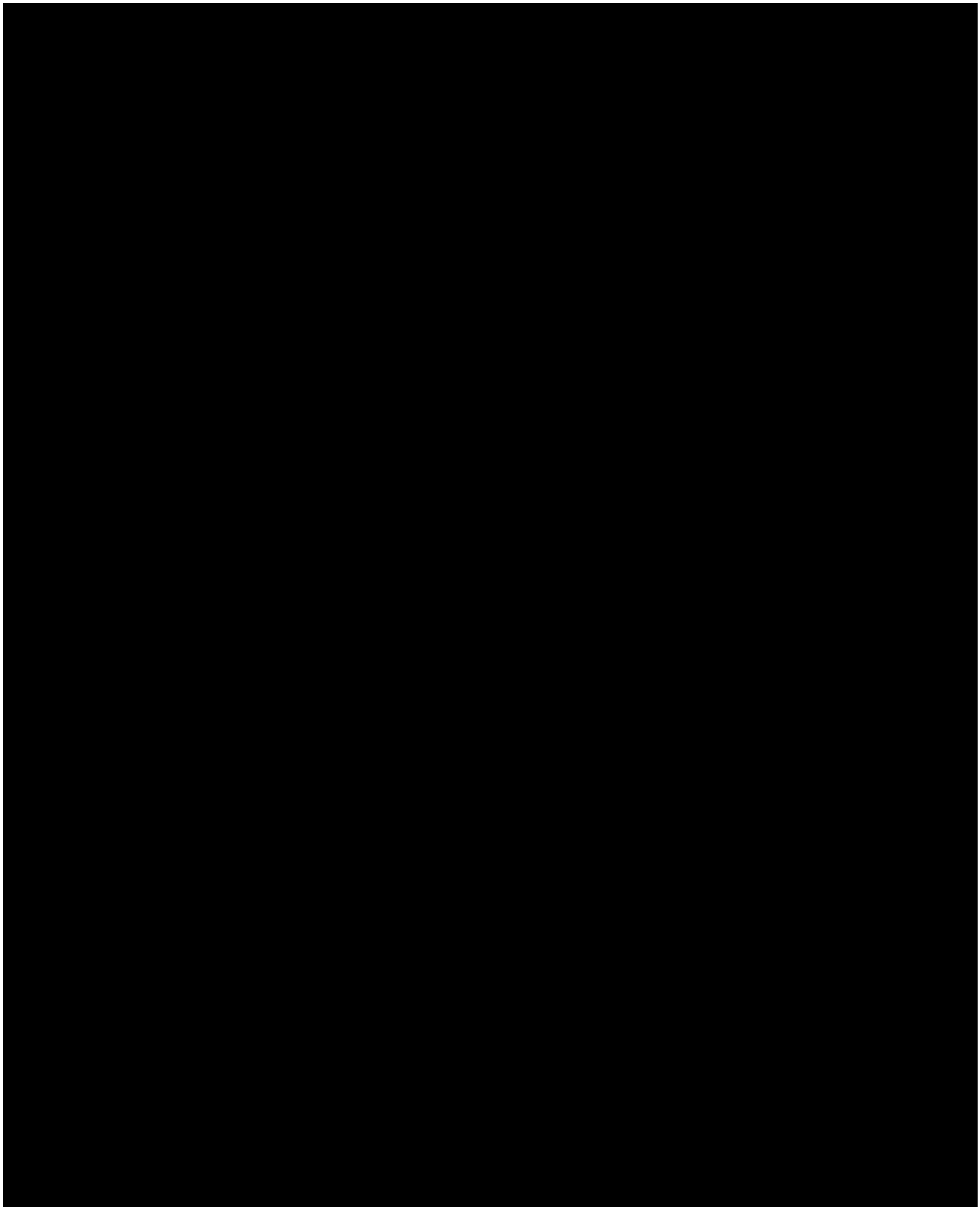
CDI excluding data after DMT switch will be used for some supportive analyses, which will not consider data collected after DMT switch date for subjects who switch DMT during the actual treatment period. A subject is considered as having this event defined here if the subject achieves CDI and does not switch DMT or if he/she switches DMT during actual treatment period but achieves CDI before the DMT switch date.

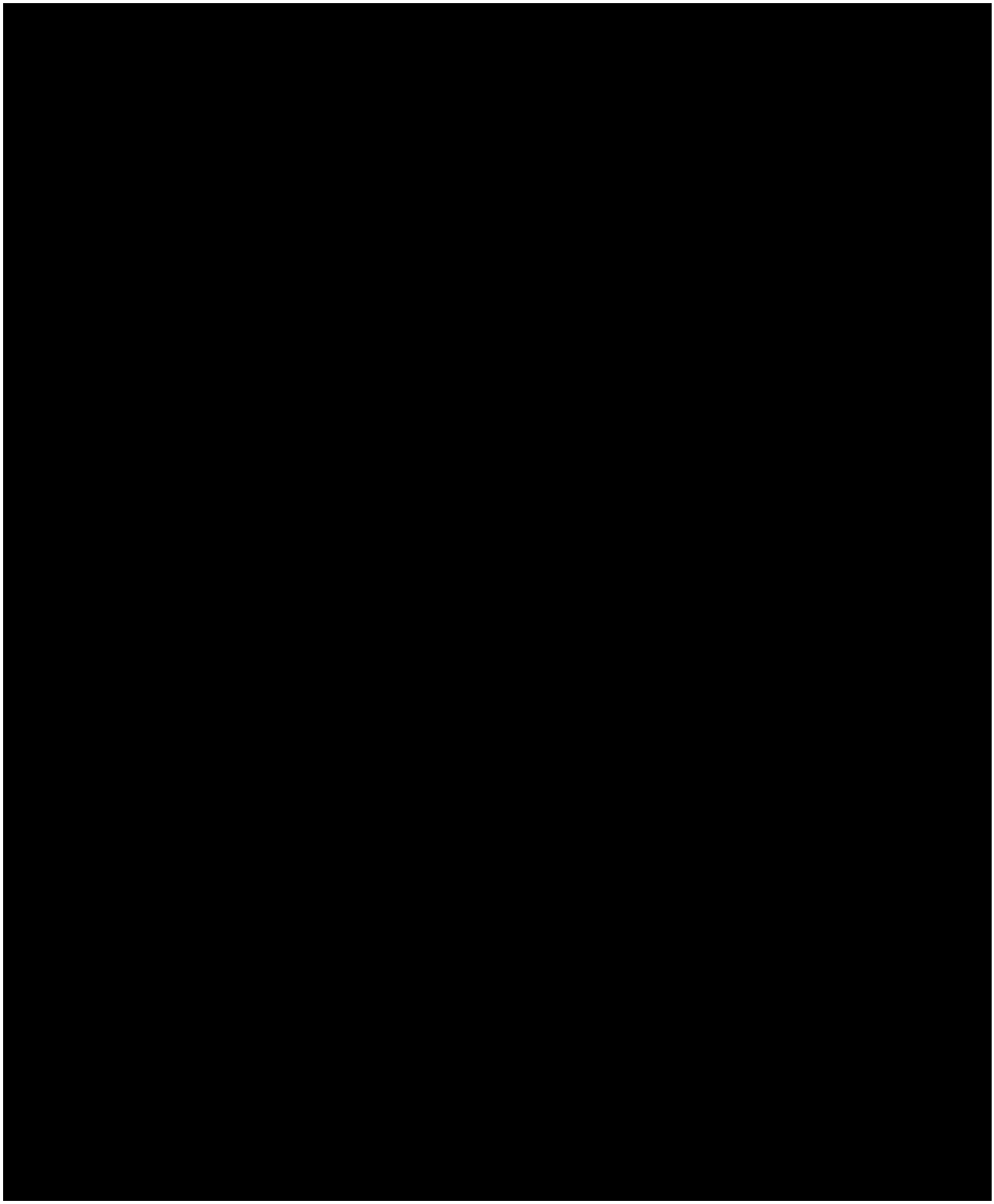
If a subject has CDI excluding data after DMT switch, the event date is the date of the CDI, otherwise the subject will be censored at the CDI censoring date, or the date of the subject's latest scheduled visit with non-missing result (including the case that the subject is unable to complete this component assessment due to MS-related physical limitations) before the DMT switch date, whichever comes earlier. The CDI event date and censoring date are as defined in Section 3.4.2.1, and DMT switch date is as defined in Section 3.2.

3.4.2.7. Tentative Improvement in Two or More Components at Week 72

If a subject has no CDI and has tentative improvement in two or more components at Week 72, but the Week 84/EOS result is missing and therefore the tentative improvement cannot be confirmed, then the subject is considered to achieve this MCE at Week 72. The time to event for

this subject is the number of days from the first dose date to the first time when tentative improvement is achieved for a component at the Week 72 visit.





3.5. Stratification Factors and Subgroup Variables

3.5.1. Stratification Factors

The randomization stratification factors are listed as follows.

- MS type:
  - Relapsing-remitting MS (RRMS)
  - Secondary progressive MS (SPMS)
- Background DMT group:
  - IFN-β (Avonex, Plegridy®, Betaferon®/ Betaseron®, or Rebif®)
  - dimethyl fumarate (DMF; Tecfidera®)
  - natalizumab (Tysabri®)

  Unless otherwise specified, the background DMT refers to the baseline DMT according to randomization stratification
- [redacted]

3.5.2. Subgroup Variables

3.5.2.1. Baseline Characteristics Subgroup Variables

- Age at baseline (≥40 and <40 years)
- Regions (North America, Eastern Europe, Western Europe and other regions)
  - North America: Canada, United States
  - Eastern Europe: Czech Republic, Hungary, Poland
  - Western Europe and other regions: Belgium, United Kingdom, Germany, France, Switzerland, Italy, Netherlands, Spain, Australia, Israel
- Baseline EDSS (≥3 and <3)
- Disease duration between onset of the first MS symptoms and randomization (≥6 years and <6 years)
- [redacted]
- [redacted]

[redacted]

- [redacted] ≥ [redacted] ≥ [redacted]
- [redacted]

3.5.2.3. DMT Subgroups

- 1-DMT groups: subjects with background DMT as 1) IFN-β, 2) Dimethyl fumarate, and 3) Natalizumab
- 2-DMT groups: subjects with background DMT as 1) IFN-β or Dimethyl fumarate, 2) IFN-β or Natalizumab, and 3) Dimethyl fumarate or Natalizumab

3.6. Analysis Population

Intention-to-treat (ITT) population, per-protocol population, [redacted], safety population, immunogenicity population, and interim analysis (IA) cohort are defined as follows:

- **ITT population**
  The ITT population is defined as all randomized subjects who received at least 1 dose of study treatment. In analyses performed on the ITT population, subjects will be analyzed according to their randomized treatment assignment regardless of actual treatment received.
- **Per-protocol population**
  The per-protocol population is defined as subjects from the ITT population who received ≥80% of planned study treatment during the period from the first dose to the ET visit date, or the last dose of study treatment in Part 1 for those who did not early terminate, did not early terminate due to sites GCP deviation, and did not have major protocol deviations that would impact the efficacy assessments. The major protocol deviations that will lead to exclusion from the per-protocol population include:
    - [redacted]
    - [redacted] ≥ [redacted]
    - meeting exclusion criterion #14 (history of suicidal ideation or an episode of clinically severe depression as determined by the Investigator within 12 weeks of enrollment; subjects receiving ongoing antidepressant therapy will not be excluded from the study unless the medication has been increased within 24 weeks prior to enrollment).
    - unblinding.

Subjects will be analyzed according to the actual treatment allocation.

- [redacted]

- **Safety population**

  The safety population is defined as all subjects who received at least 1 dose of study treatment. Although treatment assignment error is not expected, if some subjects received different study treatment than the randomization allocation, the safety analyses will be based on the actual treatment allocation. The actual treatment in Study Part 1 will be BIIB033 if the subject received any active dose of BIIB033; otherwise, the actual treatment will be placebo.

- **Immunogenicity population**

  The immunogenicity population is defined as all subjects in the safety population who had at least 1 post-dose sample evaluated for immunogenicity.

- **IA cohort**

  The IA Cohort is defined as the first 80% participants dosed in the study who have had the opportunity to complete Week 36 assessments in Study Part 1.

4. List of Planned Study Analyses

4.1. Interim Analysis

According to the protocol, in Part 1, an interim analysis (IA) may be performed by a small, independent team for futility assessment when a minimum of 50% of subjects have completed at least their Week 24 visit. This study may be terminated early if the prespecified futility criteria are met at the interim analysis. In 2019, the actual IA was performed by the Data Monitoring Committee (DMC) for futility assessment once the first 80% participants dosed in the study have had the opportunity to complete Week 36 assessments in Study Part 1. According to the prespecified criteria, futility was evaluated based on treatment effect of ORS at Week 36, as well as the overall trend and totality of data. Following the IA, the study was not stopped for futility and continued without modification. The study management team, investigators, and subjects remain blinded.

4.2. Primary Analysis

The primary analysis (PA) of the study will be conducted at the end of the placebo-controlled phase, i.e., Study Part 1, once all subjects have had the opportunity to complete the EOS visit in Part 1 or Part 2 Day 1 visit after the 72 weeks of blinded study treatment in Part 1. The PA aims to address all study objectives of Part 1, to evaluate the effects of BIIB033 versus placebo on disability improvement over 72 weeks, and assess the overall efficacy and safety of BIIB033 as an add-on therapy to anti-inflammatory DMT during this blinded, placebo-controlled study phase.

Unless otherwise specified, all the analyses specified in Section 5 are focusing on the PA in this version of the SAP.

[redacted]

5. Statistical Methods for Planned Analyses

5.1. General Principles

Descriptive summary statistics will be presented for all study primary, secondary [redacted] endpoints collected. For continuous endpoints, descriptive summary statistics will generally include number of subjects with data, the mean, standard deviation, median, interquartile range (Q1, Q3) and range (minimum, maximum). For categorical endpoints, this will generally include number and the percent of subjects with data in each category.

The statistical software, SAS® version 9.4 or above, will be used for all summaries and statistical analyses.

This Statistical Analysis Plan (SAP) document supersedes the statistical section in the protocol and provides details for those analyses pre-specified before any planned study unblinding. Additional ad hoc analyses may be conducted if needed after data unblinding and if there are any significant modification on SAP after data unblinding, those must be documented in clinical study report (CSR) accordingly.

5.2. Handling of Missing Data

5.2.1. T25FW, 9HPT-D, 9HPT-ND, PASAT-3 and SDMT

The following rules will be applied to handle missing data in T25FW, 9HPT and PASAT-3 before any further analyses or derivations of disability improvement/worsening endpoints.

At each visit, the T25FW assessment has 2 trials and the average time from the 2 trials will be used for statistical analyses.

(1) If a subject misses 1 trial due to reasons other than MS-related physical limitations, the result from the other trial will be used for that visit in the analyses.

(2) If results from both trials are missing due to reasons other than MS-related physical limitations, the T25FW assessment for that visit will be set as missing.

(3) If a subject misses either trial due to MS-related physical limitations, the assessment result (time in seconds) will be imputed as 13.7×SD (reference) + MEAN (reference), where the MEAN (reference) and SD (reference) are the mean and standard deviation of the averaged time from two trials of baseline assessments based on the reference population. The reference population is defined as all subjects dosed with non-missing baseline assessments for at least 1 trial. The baseline assessments used for calculating the

average time do not include any trials that are missing due to MS-related physical limitations.

At each visit, the 9HPT assessment will be evaluated on the dominant hand and non-dominant hand separately, and 2 trials will be performed on each hand. For each hand, the average time from the 2 trials will be used for statistical analyses.

(1) If a subject misses 1 trial on one hand due to reasons other than MS-related physical limitations, the result from the other trial will be used for that visit in the analyses.

(2) If results from both trials on one hand are missing due to reasons other than MS-related physical limitations, the 9HPT assessment for that hand will be set as missing at that visit.

(3) If a subject misses either trial on one hand due to MS-related physical limitations, 777 seconds (Fischer, J. et al. (2001)) will be assigned as 9HPT test assessment for the disabled hand at that visit.

When the average of dominant and non-dominant hand is calculated for the combined 9HPT assessment, if the assessment for one hand is missing, the average will be the assessment of the other hand.

PASAT-3 assessments are the number of correct answers. If the assessment is missing due to MS disease limitation, the assessment will be imputed as a score of 0; otherwise the assessment will be set as missing.

Symbol Digit Modality Test (SDMT) score is assessed at each visit. Measurements will not be imputed if SDMT is missing.

Additional considerations on dealing with missing data including supportive analyses are provided in Section 5.7.

5.2.2. Adverse Event and Concomitant Medication

For completely missing start dates of AEs, assign the first dose date of study treatment. No imputation will be performed for completely missing start dates of concomitant medications. The partial start dates will be imputed as follows:

- If only the day is missing and month and year are present, then assign to the first day of the month;
- If only the year is present and month and day are missing, then assign to January 1st. The imputed start date will be compared to the first dose date of study treatment. If the imputed start date is earlier than the first dose date, then the first dose date will be chosen.

No imputation will be performed for completely missing end dates of AEs and concomitant medications. The partial end dates will be imputed as follows:

- If only the day is missing and month and year are present, then assign to the last day of the month;

- If only the year is present and month and day are missing, then assign to December 31st.The imputed end date will be compared to the last day in Part 1. If the imputed end date is later than the last day in Part 1, then the last day in Part 1 will be chosen.

5.2.3. MS Relapse

For all relapses, retrieve relapses onset date from relapse assessment data and adverse event termed "Multiple sclerosis relapse" data. All relapses from relapse assessment data will be used. If there is an adverse event termed "Multiple sclerosis relapse" and the start date is different from all relapse onset dates from relapse assessment of the subject, this is considered as a subjective relapse of this subject and the start date of such adverse event is considered as the relapse onset date of a subjective relapse.

The following rules will be used to impute the completely missing or partial onset dates of all relapses:

- If the onset date is from relapse assessment:
    - If the date is completely missing, then assign to the day after the first dose date of study treatment;
    - If only the day is missing and month and year are present, then assign to the first day of the month;
    - If only the year is present and month and day are missing, then assign to January 1st;
    - The imputed onset date will be compared to the day after the first dose date. If the imputed onset date is earlier than the day after the first dose date, then the day after first dose day will be chosen.
- If the onset date is from adverse event termed "Multiple sclerosis relapse":
    - If the date is completely missing, then assign to the first dose date of study treatment;
    - If only the day is missing and month and year are present, then assign to the first day of the month;
    - If only the year is present and month and day are missing, then assign to January 1st.
    - The imputed start date will be compared to the first dose date of study treatment. If the imputed start date is earlier than the first dose date, then the first dose date will be chosen.

Protocol-defined relapse is also used for efficacy analysis. Since the protocol-defined relapse date is from relapse assessment data, the imputation will follow the rule above for imputing the onset date if the onset date is from relapse assessment.

5.3. Accounting of Subjects

The summary of subject disposition will include: subjects randomized, subjects randomized but not dosed; subjects dosed; subjects who completed the treatment in study Part 1; subjects who completed the study Part 1 (including those who completed the 72 weeks of treatment in Part 1 and signed consent for Part 2, and those who completed Week 84 visit in Part 1 and did not roll over to Part 2); subjects who completed the study Part 1 but missed one or more doses; subjects who discontinued study treatment and the reasons for discontinuation; and subjects who withdrew from study and the reasons for withdrawal. A listing of those subjects who discontinued study treatment/withdraw from study and the associated reasons for discontinuation/withdrawal will be presented by treatment group. Number of subjects in each analysis population will also be summarized. In addition, number of subjects dosed, number of subjects who completed the study in each treatment group will be summarized by country and sites. Number of subjects by background DMT group and by region will be presented by treatment groups and overall.

The summary of subjects on stratification factors (MS type, background DMT group and core group population/non-core group population) will be summarized separately by treatment groups and overall.

The number of subjects whose visits are impacted by the pandemic, including missing or out-of-window study treatment and key efficacy assessments will be summarized, according to information recorded in the study protocol deviation listing. Due to COVID-19 pandemic measures, there may be challenges to conduct on-site monitoring visits and thereof result in some study data pending source data verification (SDV). The number of subjects who have any pending SDV data and the number of study visits without SDV performed will be presented.

5.4. Demographic and Baseline Characteristics

All demographics and baseline disease characteristics will be summarized for ITT population and per-protocol population separately.

Demographic data, including age (in years), age category (<18, 18-30, 31-40, 41-50, 51-58, >58) and (<40, ≥40), and gender will be summarized by treatment groups and overall, also by treatment groups and background DMT group.

Baseline MS disease history will be summarized by treatment groups and overall, using descriptive statistics. Time since onset of MS symptoms (in years), time since MS diagnosis (in years), number of subjects with secondary progressive MS (SPMS), time since onset of secondary progressive MS (in months, for subjects with SPMS only), time since the most recent relapse prior to Day 1 (in months), [redacted], number of relapses within the past 12 months, 2 years and 3 years of enrollment will be summarized. [redacted]

Number and percentage of subjects with any MS treatment history will be summarized by treatment groups and overall. Specifically, number and percentage of subjects who have taken approved DMTs and others will also be displayed by treatment groups and overall. Approved

DMTs include alemtuzumab, cladribine, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferons (Interferon Beta-1A(AVONEX), Interferon Beta-1A (REBIF), Interferon Beta-1B (EXTAVIA)), Interferon Beta-1B (BETASERON), Peginterferon Beta-1A (PLEGRIDY)), natalizumab, ocrelizumab, and teriflunomide.

[redacted]

Medical history will be coded using the latest version of MedDRA (version 23.0 or later if updated) and number and percentage of subjects with each history will be presented using the preferred term.

5.5. Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a protocol deviation log and categorized as major or minor deviations. Number and percentage of subjects with at least one major deviation will be summarized by category. All protocol deviations related to COVID-19 pandemic measures will be provided in a listing with all available details.

5.6. Study Treatment Exposure and Concomitant Medications

Extent of exposure to study treatment will be summarized for both the ITT and the per-protocol populations. Number of infusions taken will be summarized as both continuous and category variables (>=12, >=16, >=18). The overall study drug compliance and study drug compliance during treatment phase will be provided. Subjects will also be categorized and summarized by "without missing any dose", "missed one dose" and "missed >1 dose".

Overall study drug compliance

Defined as the percentage of study drug infusions actually received over 19 planned doses for 72 weeks, will be summarized regardless of study completion for all subjects.

Study drug compliance during treatment phase

Defined as number of infusions actually received divided by the number of expected; the expected infusions is the total 19 planned doses for those who completed 72 weeks of study treatment, and is the total number of planned doses before early termination visit date for those who early terminated.

In the study Part 1, no subject with study treatment administration is impacted by COVID-19 infection or COVID-19 pandemic measures. Therefore, no additional summary on the extent of exposure to study treatment will provided for COVID-19 impact.

The total number of weeks on study drug for each subject will be summarized as a continuous variable and presented in groups of 12-week intervals. Weeks on study drug are calculated as the number of weeks from the first dose date to the last dose date plus 4 weeks. Days on study drug are calculated as the number of days from the first dose date to the last dose date plus 28 days.

Concomitant therapy will be summarized for both the ITT and the per-protocol populations.

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary (WHODD GLOBAL version B3 March 2020, or later if updated). Concomitant medication is any drug or substance administered between the time the subject signed the ICF and the EOS date. A concomitant non-drug treatment is any therapeutic interventions or diagnostic assessment performed between the time the subject signed the ICF and the EOS date.

A medication in Part 1 refers to a medication that starts prior to the study treatment infusion in Part 2 Day 1 visit. If a subject is not enrolled in Part 2 or is enrolled in Part 2 but never receives infusion of study treatment in Part 2, all t medications will be considered as occurring in Part 1.

A medication and/or non-drug treatments in Part 1 is regarded as concomitant with study treatment in Part 1 of the study if the stop date/time is on or after the first dose date/time of study treatment. In order to determine whether medication and/or non-drug treatments with missing stop dates are concomitant, the following additional criteria will be used:

- If stop date of a particular therapy has year, month available but day missing and the year and month of the stop date is on/after the first dose date, then the therapy will be considered as concomitant;
- If stop date of a particular therapy has year available but month and day missing and the year is on/after the first dose date, then the therapy will be considered as concomitant.

If stop date of a particular therapy is missing, then the therapy will be considered as concomitant. The number and percent of subjects taking concomitant medication and non-drug treatments will be summarized separately by treatment group and overall.

5.7. Efficacy Endpoints

5.7.1. General Analysis Methods for Efficacy Endpoints

All efficacy endpoints will be evaluated in the ITT population as defined in Section 3.6. The primary and secondary efficacy endpoints will also be analyzed in the per-protocol population as supportive analysis.

Subjects who early terminated due to sites GCP deviation will not be used for any efficacy analysis.

For data that are analyzed by longitudinal analysis, efficacy endpoint assessments at unscheduled visits can be used. This includes the primary endpoint ORS [redacted] in which data are analyzed by longitudinal analysis. It is possible that the assessments at an unscheduled visit can be used for summary by visit through mapping visit windows (Section 3.2). For efficacy data that are summarized by visit and used in longitudinal analysis, assessments from all scheduled visits including ET visit and EOS visit, as well as all unscheduled visits, will be mapped to an appropriate analysis visit using a windowing scheme (Section 3.2).

Study protocol specifies that disallowed concomitant therapies include: 1) more than one background DMT at any time, including any chronic immunosuppressant or immunomodulatory therapy; 2) any investigational product; 3) any systemic steroid therapy without prior approval from the Sponsor, except for protocol-defined treatment of relapses. The blinded clinical review

of all concomitant therapies data collected during Part 1 of the study shows that one subject received immunosuppressant treatment (methotrexate) as a concomitant medication during the Part 1. No subject received investigational therapy. Although in Part 1 there were subjects who received systemic steroid treatments for various medical reasons but not for protocol-defined relapses, all cases were a single course for one week or less during the entire Part 1, which were considered to have minimal impact on the efficacy analyses. Therefore, in the efficacy analyses, only immunosuppressant treatment (methotrexate) is considered as prohibited concomitant therapy in Part 1. Data on efficacy endpoints of a study subject collected after the use of methotrexate will not be included in any efficacy analyses for this subject.

In general, baseline disability measurements used in model covariates refer to the continuous variables of baseline results of the disability assessments that serve as the independent component endpoint or constitute the MCE to be used as the dependent variable in the models (MMRM, logistic regression, Cox proportional hazard model, etc.). For analyses of primary and secondary MCEs, baseline EDSS, baseline T25FW time, baseline 9HPT-D time, baseline 9HPT-ND time, baseline PASAT-3 score and baseline SDMT score as continuous covariates will be included in the statistical model when the model dependent variable includes the corresponding disability assessments. The exception is that in the supportive analysis of repeating MMRM analysis on the overall response score using ITT population with combined 9HPT, the average of baseline 9HPT-D time and baseline 9HPT-ND time as a continuous covariate will be included in the statistical model, instead of including both baseline 9HPT-D time and baseline 9HPT-ND time. For analyses of individual components, the corresponding baseline measurement (EDSS, T25FW, 9HPT-D, 9HPT-ND, PASAT-3, SDMT, [redacted]) will be used as continuous covariate in the model. Unless otherwise specified, all analysis models are adjusted for stratification (categorical) variables of background DMT group [redacted]. Though MS type was also used as a stratification factor in the randomization, it will not be included in any statistical models as an adjusted covariate. This is because after completion of randomization of all subjects, only two out of all 263 enrolled subjects are with SPMS, therefore, including such adjustment will have minimal impact on the statistical analysis results.

Mixed Model for Repeated Measures (MMRM) will be used to analyze longitudinal assessment for continuous endpoints. MMRM will have treatment, visit, treatment-by-visit interaction as independent variables, adjusting for baseline disability measurements and stratification variables of background DMT group [redacted]. Least-squares (LS) adjusted mean is constructed using observed margin. An unstructured (UN) covariance matrix will be assumed to model the within-subject variability. Model convergence will be checked. If the MMRM with unstructured covariance matrix fails to converge, a compound symmetry (CS) structure will be used. LS adjusted mean and its 95% CI of each treatment group as well as treatment differences between BIIB033 vs. placebo will be displayed with 95% CI and p-values.

Logistic regression will be used to analyze and compare the proportion of CDI (defined in Section 3.4.2.1) or CDW (defined in Section 3.4.2.2) with logit link function. The model will have treatment as independent variable, adjusting for baseline disability measurements and stratification variables of background DMT group [redacted]. Odds ratio of BIIB033 group vs. placebo group with 95% confidence interval (CI) and p-value will be

presented. In the situation that logistic regression model fails to converge, stratification variables (background DMT group [redacted]) will be removed from the covariate list and the logistic regression model will be fitted again. If the logistic regression model still fails to converge, the p-value from Fisher's Exact Test will be presented instead of logistic regression model estimates. Ordinal logistic regression will be used for ordinal data, which will adjust for variables similar as described above for logistic regression. Odds ratio of BIIB033 vs. Placebo with 95% CI and p-value will be presented.

Cox proportional hazards model will be used to analyze and compare time to the first CDI or CDW assuming the hazard ratio is constant over time. The model will include treatment as independent variable, adjusting for baseline disability measurements, and stratification variables of background DMT group [redacted]. Hazard ratio of each BIIB033 vs. placebo with 95% CI and p-value will also be presented. In the situation that Cox proportional hazards model fails to converge, stratification variables (background DMT group [redacted]) will be removed from the covariate list and the Cox proportional hazards model will be fitted again.

Analysis of covariance (ANCOVA) model will be used to analyze and compare change from baseline for some continuous endpoints. The model will have treatment as the independent variable, adjusting for baseline disability measurements and stratification variables (background DMT group [redacted]). Based on Type III sum of squares, LS adjusted mean of each treatment group as well as treatment difference between BIIB033 vs. placebo will be presented with 95% CI and p-values.

There are no missing data through Week 72 due to COVID-19 or COVID-19 pandemic measures. A small number of subjects have missing assessments at the Week 84 or Part 2 Day 1 visit, which would be used to confirm any tentative improvement or worsening events in the treatment period. In the main analysis, subjects with tentative improvement or worsening events before Week 84 or Part 2 Day 1 visit will not be considered as having a confirmed event. Supportive analysis will be conducted by considering these subjects having a confirmed event. Data with pending SDV due to COVID-19 will be included in analysis.

5.7.2. Primary Efficacy Endpoint

5.7.2.1. Main Analysis of Primary Efficacy Endpoint

For each subject at each post-baseline visit during the treatment period (Weeks 12, 24, 36, 48, 60 and 72), an overall response score (ORS) as defined in Section 2.1.2 will be determined based on all components (EDSS, T25FW, 9HPT-D and 9HPT-ND).

The ORS will be summarized using descriptive summary statistics by visit. MMRM will be used to analyze the overall response scores up to Week 72. The MMRM model will include treatment, visit, treatment-by-visit interaction, baseline disability measurements (EDSS, T25FW, 9HPT-D and 9HPT-ND), background DMT group [redacted] as fixed effects. LS adjusted mean of each treatment group and the treatment difference between BIIB033 vs. placebo will be presented with associated 95% CI and p-value at Weeks 12, 24, 36, 48, 60 and 72. LS adjusted means by treatment group will also be displayed graphically by visit. The treatment effect between BIIB033 vs. placebo over 72 weeks will be estimated as the average

treatment effect across the visits through 72 weeks derived from the model, based on which the p-value using the T-test statistic for the primary null hypothesis will be reported. If the average treatment effect is significant at α level of 0.05 (2-sided), treatment difference at individual timepoints (visits) will also be assessed based on the same model.

For the interim analysis of the overall response score, see Section 5.11 for details.

5.7.2.2. Supportive Analyses for Primary Efficacy Endpoint

The following supportive analyses will be conducted. Since all subjects would have had their Week 72 assessments done before start of the COVID-19 pandemic measures, no supportive analysis will be performed related to COVID-19.

(1) The same MMRM analysis for the ORS as described in Section 5.7.2.1 will be repeated for the per-protocol population.

(2) The same MMRM analysis for the ORS will be repeated in the ITT population with combined 9HPT scores from the dominant and non-dominant hand. The average of 9HPT-D and 9HPT-ND is calculated for 9HPT assessment, considering the high correlation between two hands. Then the range of overall response score will be -3 to +3. If the assessment for one hand is missing after imputation rule is applied, the average will be the assessment of the other hand.

(3) The same MMRM analysis for the ORS will be repeated using 20% thresholds for improvement and worsening in T25FW, 9HPT-D and 9HPT-ND.

(4) MMRM analysis on the ORS will be repeated in the ITT population with multiple imputation for missing values of EDSS, T25FW, 9HPT-D and 9HPT-ND over 72 weeks of treatment under the assumptions of missing at random. Each individual component in the composite overall response will be multiply imputed as a continuous variable with treatment group, randomization stratification factors (excluding MS type) and baseline scores of EDSS, T25FW, 9HPT-D and 9HPT-ND assessments included in the imputation model. The missing baseline value will be imputed by the mean baseline in corresponding treatment group. Multiple imputations will be performed using PROC MI in SAS assuming the scores at post-baseline visits following a joint multivariate normal distribution. After imputing the individual component scores, the overall response score at each visit will then be calculated using the imputed component scores in each imputed data set following the definition in Section 2.1.2. A set of 500 imputed data sets will be generated with 200 burn-in iterations and the relative efficiency parameter will be checked to ensure no extreme values are sampled. The multiply imputed datasets will be analyzed using the same MMRM model for the ORS, and the estimates from all imputed datasets will be combined for an overall inference using Rubin's rule.

(5) The same MMRM analysis for the ORS will be repeated in the ITT population by excluding data collected after the end of actual treatment period (i.e., after treatment discontinuation) for subjects discontinued study treatment early but still stayed in the study and continued with study assessments.

(6) The same MMRM analysis for the ORS will be repeated in the ITT population by excluding data collected after DMT switch date for subjects who switched DMT during the actual treatment period.

5.7.2.3. Subgroup Analysis of Primary Efficacy Endpoint

Subgroup analysis will be performed for the primary efficacy endpoint on the subgroups defined in Section 3.5.2, including baseline characteristics subgroups, [redacted], DMT subgroups. All the subgroup analyses will be performed in each subgroup separately. A subgroup variable will not be used in the model covariates for the analysis performed on the subgroups defined by that subgroup variable. Within each subgroup, the MMRM analysis for the ORS will be performed as described in Section 5.7.2.1. Subgroup analyses aim to assess the consistency of treatment effect across subgroups. [redacted]

5.7.3. Secondary Efficacy Endpoints and Related Time to Event Endpoints

5.7.3.1. Main Analysis for Proportion of CDI on MCE

The number and percentage of subjects with CDI for the secondary MCE based on EDSS, T25FW, 9HPT-D and 9HPT-ND, as defined in Section 3.4.2.1, will be displayed by treatment groups.

A logistic regression model for proportion of CDI will be performed with treatment as independent variable, adjusting for baseline disability measurements and stratification variables of background DMT group [redacted]. The odds ratios of BIIB033 vs. placebo from the logistic regression model will be presented with 95% CI and p-value.

5.7.3.2. Supportive Analyses for Proportion of CDI in MCEs

The following supportive analyses will be conducted on secondary endpoints: proportion of subjects with 12-week CDI in MCEs based on EDSS, T25FW, 9HPT-D, 9HPT-ND, with default threshold (15%) and with 20% thresholds for T25FW and 9HPT.

(1) The main analysis as described in Section 5.7.3.1 will be repeated for the per-protocol population.

(2) The main analysis will be repeated by including CDI and tentative improvement in two or more components at Week 72 (defined in Section 3.4.2.7)

(3) The main analysis will be repeated for proportion of subjects with CDI in two or more components (defined in Section 3.4.2.5)

(4) Confirmed improvement extent analysis:

The confirmed improvement extent endpoint is defined as the number of CDI per subject based on whether a subject has CDI in EDSS, T25FW, 9HPT-D, or 9HPT-ND (using the same criteria defined in Section 3.4.2.1). Specifically, the confirmed improvement extent is defined as follows:

- Extent=0: CDI in none of the 4 components

- Extent=1: CDI in 1 of the 4 components
- Extent=2: CDI in 2 or more of the 4 components

The number and percentage of subjects by confirmed improvement extent will be displayed. The ordinal logistic regression will be used to analyze the probability of different confirmed improvement extent. Proportional odds assumption is assumed. That is, the effect of covariates and treatment is the same for different logit function (extent=0 vs. extent=1 or 2, or extent=1 or 2 vs. extent=0). The common odds ratio of BIIB033 vs. placebo will be displayed with 95% CI and p-value.

(5) The main analysis will be repeated for CDI considering unconfirmed events due to COVID-19. To evaluate COVID-19 impact, if the subject has tentative improvement in at least one component at Week 72, but the subsequent planned visit to be used for confirmation (Week 84/EOS or Part 2 Day 1) is not conducted, or the corresponding disability assessment is not done due to COVID-19 or COVID-19 pandemic measures, then tentative improvement would be assumed to be confirmed for the component and hence for the MCE.

(6) The main analysis will be repeated for CDI excluding data after DMT switch (defined in Section 3.4.2.6).

5.7.3.3. Subgroup Analysis for Proportion of CDI in MCEs

Subgroup analysis will be performed for the secondary efficacy endpoints: proportion of subjects with 12-week CDI in MCEs based on EDSS, T25FW, 9HPT-D and 9HPT-ND, with default threshold (15%) and with 20% thresholds for T25FW and 9HPT separately, on the pre-defined subgroups in Section 3.5.2.

Logistic regression will be used for all subgroup analyses on secondary MCEs. The probability of CDI will be analyzed and compared in each subgroup. The logistic regression model will be similar to the one used in the main analysis for CDI in MCE, except that a subgroup variable will be excluded from the model covariates for the analysis performed on the subgroups defined by that subgroup variable. In subgroup analysis of two DMT groups, the background DMT to be included in the model covariates is the actual DMT at baseline instead of background DMT per randomization stratification. Odds ratio of BIIB033 vs. placebo for each subgroup will be displayed with 95% CI and p-value.

5.7.3.4. Main Analysis for Time to CDI and CDW

For the time to CDI and time to CDW endpoints described in Section 2.1.6.2 supporting analyses on other clinical disability measures, the following analyses will be performed. The Kaplan-Meier (K-M) curve will be used to display distribution of time to CDI (or CDW) event. Treatment effect on time to first CDI (or CDW) event will also be analyzed based on a Cox proportional hazards model with treatment as the independent variable, adjusting for baseline component measurements, and stratification variables of background DMT and baseline MTR/DTI category. Hazard ratio of BIIB033 vs. placebo will be displayed with 95% CI and p-value.

5.7.3.5. Supportive Analyses for Time to CDI in MCEs

The following supportive analyses will be conducted on time to 12-week CDI in MCEs based on EDSS, T25FW, 9HPT-D and 9HPT-ND, with default threshold (15%) and with 20% thresholds for T25FW and 9HPT, separately.

(1) The main analysis described in Section 5.7.3.4 will be conducted using per-protocol population.

(2) The main analysis will be repeated by including CDI and tentative improvement in two or more components at Week 72 (defined in Section 3.4.2.7).

(3) The main analysis will be repeated based on the CDI in two or more component defined in Section 3.4.2.5.

(4) The main analysis will be repeated for CDI considering unconfirmed events due to COVID-19. To evaluate COVID-19 impact, if the subjects have tentative improvement on at least one component at week 72, but the subsequent planned visit to be used for confirmation (Week 84/EOS or Part 2 Day 1) is not conducted, or the corresponding disability assessment is not done due to COVID-19 or COVID-19 pandemic measures, then tentative improvement would be assumed to be confirmed for the component and hence for the MCE.

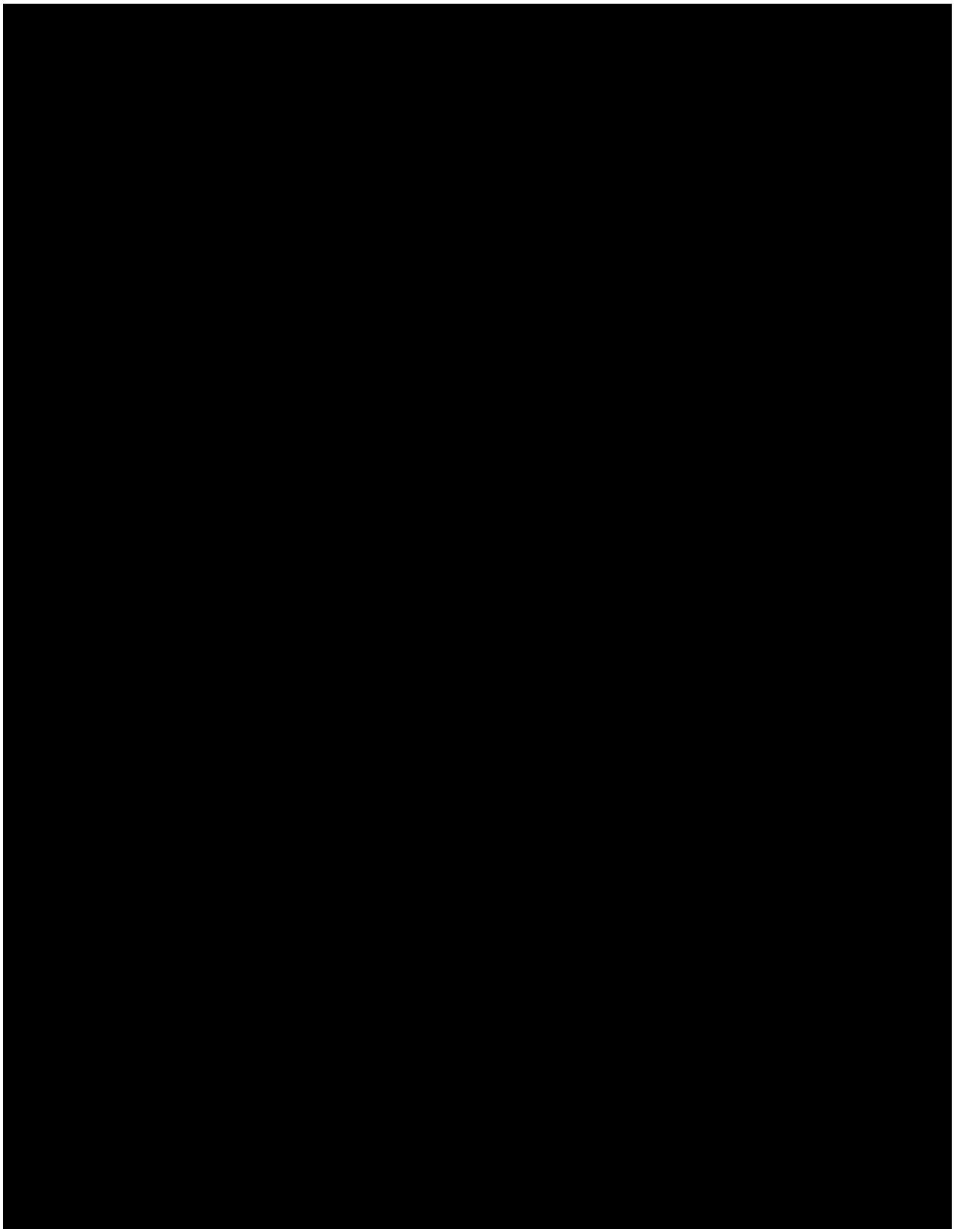
(5) The main analysis will be repeated for CDI excluding data after DMT switch (defined in Section 3.4.2.6).

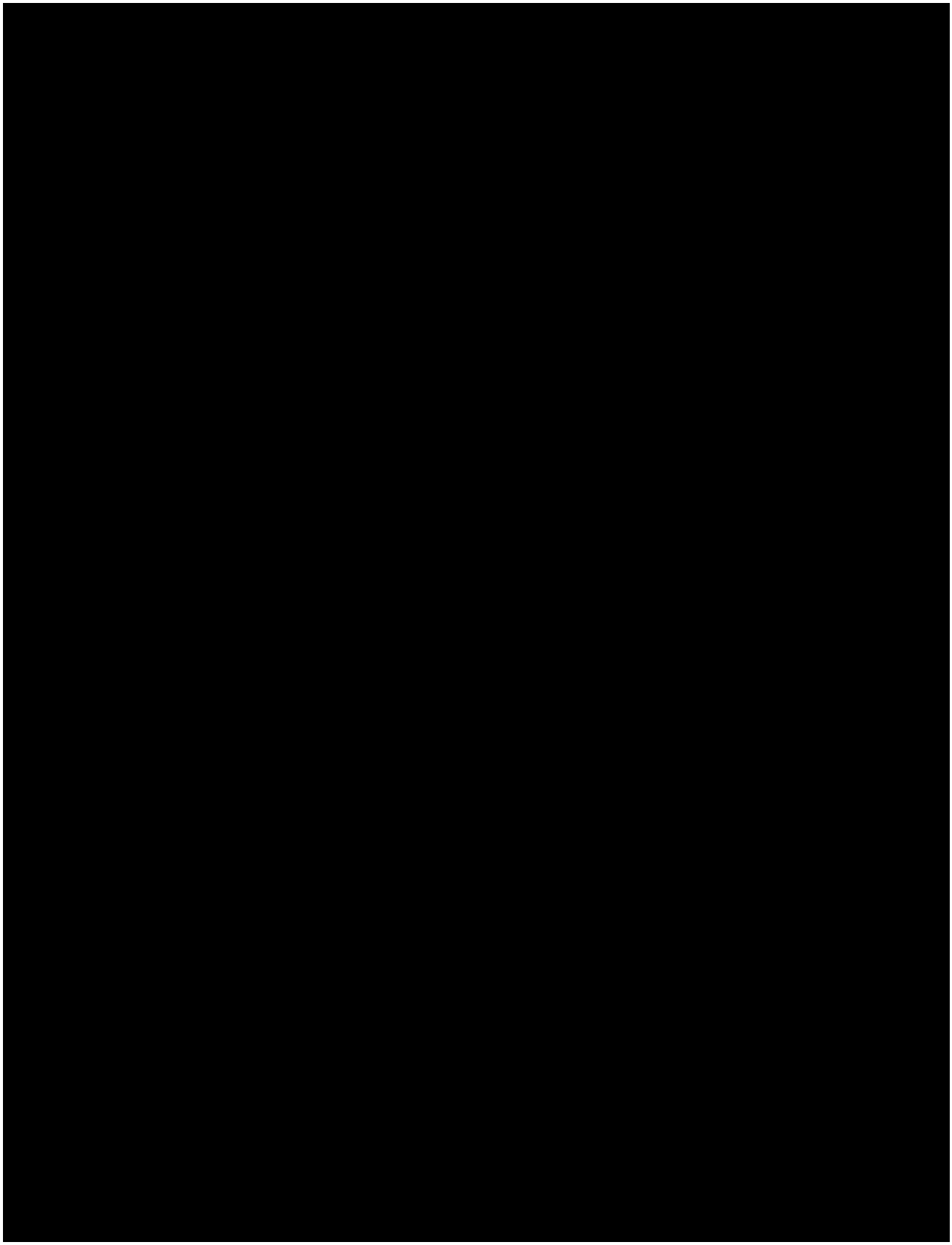
5.7.3.6. Subgroup Analysis for Time to CDI

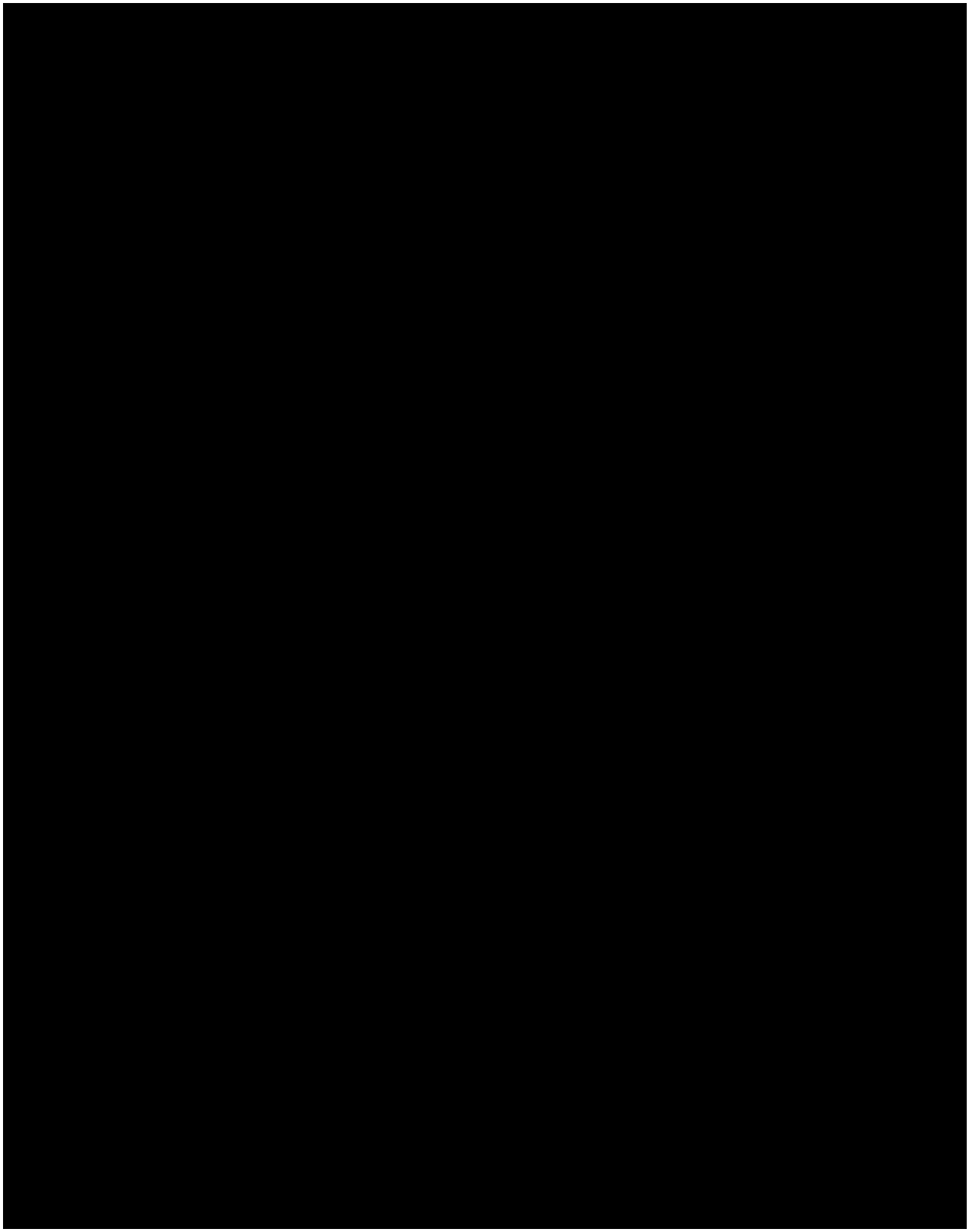
Subgroup analysis will be performed for the time to event endpoints for 12-week CDI for MCEs based on EDSS, T25FW, 9HPT-D, 9HPT-ND, with default threshold (15%) and with 20% thresholds for T25FW and 9HPT separately, on the pre-defined subgroups in Section 3.5.2.

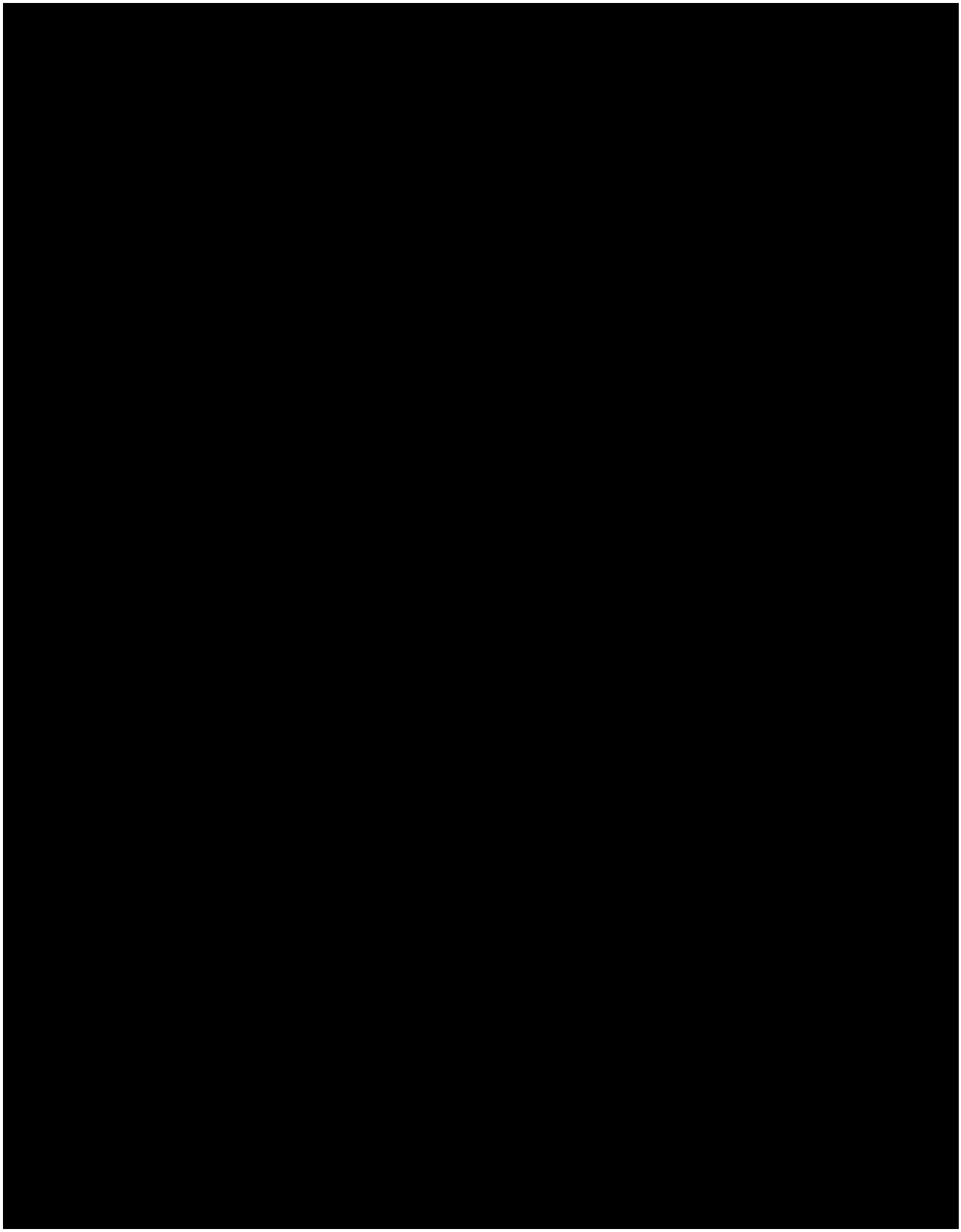
The analysis similar to the main analysis described in Section 5.7.3.4 will be performed in each subgroup. The Cox regression model will be similar to the one used in the main analysis for time to CDI in MCE, except that a subgroup variable will be excluded from the model covariates or strata variables for the analysis performed on the subgroups defined by that subgroup variable. In subgroup analysis of two DMT groups, the background DMT group to be included in the model covariates is the actual background DMT group instead of background DMT group used for randomization/stratification. Hazards ratio of BIIB033 group vs. placebo group will be displayed with 95% CI and p-value.

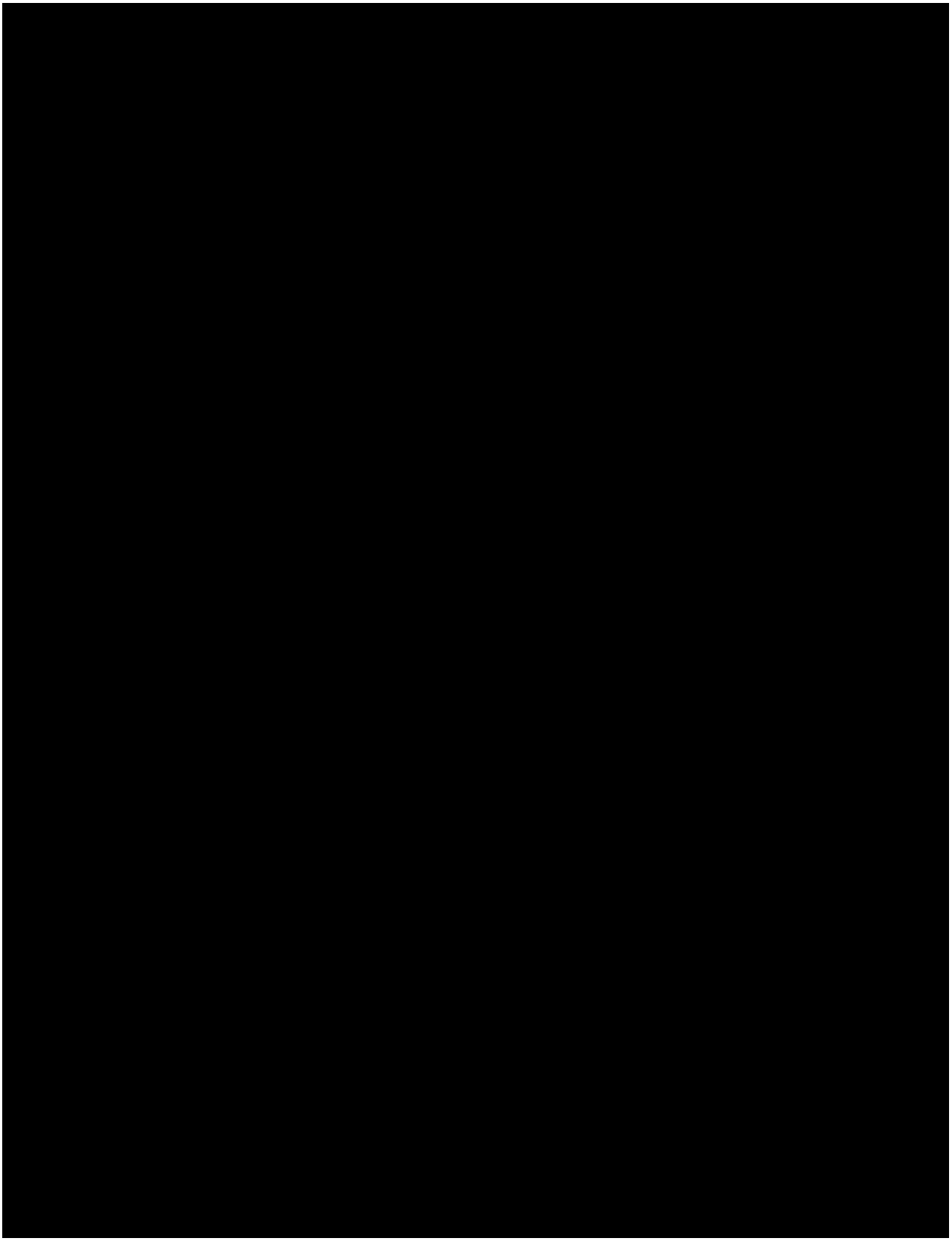
[redacted]











[redacted]

5.8. Safety Endpoints

5.8.1. General Analysis Methods for Safety Endpoints

All safety endpoints will be evaluated in the safety population (all subjects dosed) as defined in Section 3.6.

All treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), clinical laboratory abnormalities, vital sign measurements, physical examination findings, 12-lead ECG readings, MS signs and symptoms, annualized relapse rate, body weight and Columbia Suicide Severity Rating Scale (C-SSRS) will be evaluated for safety. Safety data collected by Follow-up visit (EOS visit (Week 84 or earlier for early termination subjects) for those who are not enrolled in Part 2, or Part 2 Day 1 visit for those who enroll in Part 2 of the study) will be summarized using descriptive statistics by treatment groups. For subjects who do not enroll in Part 2, the safety data collected by EOS visit will all be used; for subjects who are enrolled in Part 2, if a safety data has both date and time, the date and time will be compared with Part 2 Day 1 infusion day and time and any data that is collected on or after the Part 2 Day 1 infusion day and time is excluded from analysis; if a safety data has date but does not have time, the data that is collected on or after Part 2 Day1 is excluded from analysis. If a subject is enrolled in Part 2 but does not receive Part 2 Day 1 infusion, all safety data up to Part 2 Day 1 visit last date will be used.

For safety data that are summarized by visit, assessments from all scheduled visits, ET visit, EOS visit and unscheduled visits in Part 1 will be mapped to an appropriate analysis visit using a windowing scheme (Section 3.2).

5.8.2. Adverse Events

For this study, any TEAE experienced by the subject between the time of first dose of study treatment (Day 1/Baseline) and the EOS visit in Part 1 for those who do not enroll in Part 2 or Part 2 Day 1 - 1 for those who enroll in Part 2 is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. Any SAE experienced by the subject between the time the subject has signed the ICF and the EOS visit in Part 1 for those who do not enroll in Part 2 or Part 2 Day 1 - 1 for those who enroll in Part 2 is to be recorded, regardless of the severity of the event or its relationship to study treatment.

All AEs will be coded using MedDRA (version 23.0 or later if updated) and will be analyzed based on the principle of treatment emergence.

In order to define treatment-emergent AEs with completely missing/partial start or end dates, the following additional criteria will be used:

- If both the start and end dates for a particular event are completely missing, then that event is considered treatment emergent;
- If the start date for a particular event is completely missing, then the end date/time will be compared to the first dose date:

  - If the end date/time is complete and is on or after the first dose date/time, then that event is considered as treatment emergent;
  - If the end time is missing, but the end date is present and is on or after the first dose date, then that event is considered as treatment emergent;
  - If the end day is missing, but the year/month of end date is present and is on or after that of the first dose date, then that event is considered as treatment emergent;
  - If only the year of end date is present and is on or after that of the first dose date, then that event is considered as treatment emergent;
- If the start date for a particular event is partially missing, and the year/month/day of the event date will be compared to that of the first dose date:
  - If the start time is missing and year/month/day of the start date falls after that of the first dose date, then that event is considered treatment emergent;
  - If the start day is missing and year/month of the start date falls after that of the first dose date, then that event is considered treatment emergent;
  - If only the year of the start date is present and falls after that of the first dose date, then that event is considered as treatment emergent.
  - If the partial start date is the same as that of the first dose date, then the end date/time will be compared to the first dose date following the logic above.

The overall summary table of TEAEs will present the number of subjects with the following events by treatment groups. A subject is counted only once in each category. All treatment-emergent adverse event and treatment-emergent serious adverse events will be presented and summarized.

- Any TEAE;
- TEAE with severity as “moderate” or “severe”;
- TEAE with severity as “severe”;
- Current DMT related TEAE;
- Study treatment related TEAE;
- Any SAE;
- Current DMT related SAE;
- Study treatment related SAE;
- AE leading to discontinuation of study treatment;
- AE leading to withdrawal from study.

The incidence of TEAEs will be summarized using the primary system organ class (SOC) and preferred term (PT). Preferred terms are presented by decreasing incidence in the BIIB033 column within each system organ class.

The incidence of TEAEs will also be summarized by event severity and by relationship to study drug using system organ class and preferred term. Within each system organ class or/and preferred term, the same subject will be counted only once. Under the same system organ class or/and preferred term, the occurrence of the adverse event with the greatest severity will be used in the calculation of incidence by severity; the occurrence of the adverse event with the strongest relationship to study drug will be used in summarizing incidence by relationship to study drug.

Additionally, the incidence of TEAEs will be summarized by using preferred term only, and preferred terms will be ordered by decreasing frequency of AEs in the BIIB033 column.

The incidence of treatment-emergent SAEs will also be summarized by primary system organ class, preferred term and treatment group as well.

Listings of AEs, SAEs, AEs that led to study drug discontinuation, and AEs that led to study withdrawal will be presented. Listing of death will be provided if applicable.

In some AE/SAE listings, complete AE start and end dates are needed to calculate the relative study days of AE start and end. Therefore, any partial date will be imputed for these listings as described in Section 5.2.2.

AEs around the time of infusion

The incidence of AEs around the time of the infusion (within 4 hours and 24 hours post start of infusion respectively) will be summarized by preferred term and visit for each treatment group. At each visit, the same subject will be counted only once within each preferred term. Preferred terms will be ordered by decreasing frequency of AEs in the BIIB033 column.

Listings of such AEs around the time of the infusion (within 4 hours and 24 hours after infusion start respectively) will be provided by treatment group.

5.8.3. MS Relapse

If an MS relapse is suspected during the study, an unscheduled visit should be performed to confirm the relapse and assess the severity, which will be documented in the relapse assessment form.

Summary will be made for all relapse (including protocol-defined, non-protocol-defined, and subjective relapse) as well as protocol-defined relapse only. A summary table will be displayed with the number of subjects with 0, 1, 2, 3 or >3 relapse by treatment groups. The total number of relapse and subject-years followed will be shown in the table. Total number of subject-year is defined as the sum of number of days of all subjects in the study divided by 365.25. Unadjusted annualized relapse rate is the total number of relapses of all subjects in the study divided by the total subject-year.

5.8.4. Clinical Laboratory Abnormalities

The following clinical laboratory parameters are assessed at all study visits as stated in Section 5 and Section 14.2 of the protocol (except that baseline assessments do not need to be repeated if Screening is within 7 days of Baseline):

- Hematology: complete blood count with differential and platelet count, and absolute neutrophil count. Prothrombin time (PT), partial thromboplastin time (PTT) and platelets will also be measured for all subjects at screening
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), gamma-glutamyl-transferase (GGT), glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium and follicle-stimulating hormone (FSH: for postmenopausal female subjects only)
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal)
- Serum and urine pregnancy test (women of child-bearing potential only)

Baseline value is defined as in Section 5.1.

Shift analyses

Laboratory data (except coagulation) will be summarized using shift tables where appropriate. Each subject's hematology and blood chemistry values will be flagged as "low", "normal", or "high" based on the normal ranges of the central laboratory or as "unknown" if no result is available. Each subject's urinalysis values will be flagged as "positive" (or "low"/"high"), "negative" (or "normal"), or "unknown". Shifts from baseline to high or low status for hematology and blood chemistry parameters, and shifts from baseline to high or positive status for urinalysis will be presented.

In the hematology and blood chemistry shift summary tables, entries are numbers of subjects shift to low (or high) divide by number of subjects at risk followed by corresponding percentages. Number at risk for shifting to low (or high) is the number of subjects whose baseline value was not low (or high) and who had at least one post-baseline evaluation. Shift to low includes normal to low, high to low, and unknown to low. Shift to high includes normal to high, low to high, and unknown to high.

In the urinalysis shift summary table, entries are numbers of subjects shift to high or positive divided by number of subjects at risk followed by corresponding percentages. Number at risk for shift to high or positive is the number of subjects whose baseline value was not high or positive and who had at least one post-baseline evaluation. Shift to high or positive includes low to high, normal or negative to high or positive and unknown to high or positive.

The following rule will be used to determine the abnormality for urine test result of "Trace".

- For Urine Blood test, if subject is female and test result is "Trace", then it is considered as Normal/Negative;

- For other urine tests, if test result is "Trace", then it is considered as High/Positive.

A listing will be presented for all subjects with post-baseline urinalysis shifts. In this listing, each subject's complete values for that specific urine test from screening to last study visit will be listed with shifts labeled.

Liver function laboratory tests

For liver function laboratory tests (ALT, AST, and total bilirubin), count and percentage of maximal post-baseline values by following categories will be provided:

For ALT or AST,

- ≤ Upper Limit of Normal (ULN),
- >ULN,
- ≥ 3x ULN,
- >5x ULN,
- >10x ULN,
- >20x ULN.

For total bilirubin,

- ≤ ULN,
- >ULN,
- ≥ 1.5x ULN,
- >2x ULN.

For more than one liver function test

- ALT or AST ≥ 3x ULN and total bilirubin ≥ 1.5x ULN at the same time point,
- ALT or AST ≥ 3x ULN and total bilirubin >2x ULN at the same time point.

A subject listing will be presented for all subjects with any post-baseline ALT or AST ≥ 3x ULN. In this listing, each subject's detailed liver function test values (total bilirubin, alkaline phosphatase, ALT/SGPT, AST/SGOT, GGT) from screening to last study visit will be listed with abnormal records labeled.

Summary and listings of actual values and change from baseline

Actual laboratory values, changes from baseline and percent changes from baseline in selected quantitative laboratory values will be summarized using descriptive statistics by treatment group and visit. Box and whisker plots displaying values and changes from baseline by visit will also be presented.

Potentially clinically significant (PCS) abnormalities

For hematology and blood chemistry, the number and percentage of subjects with any post-baseline PCS laboratory abnormalities will be summarized by treatment group for the parameters provided in **Table *2***.

Subject listings will also be presented for all subjects with any PCS laboratory abnormalities. In these listings, each subject's complete history from screening to last study visit for that specific laboratory test meeting the PCS criteria will be listed; any abnormal values based on the normal ranges of the central laboratory and abnormal values based PCS criteria will be separately flagged in the same listing.

Table 2: Laboratory PCS Criteria (Adult)

Parameter Name	Unit	PCS Low	PCS High
Hematology			
White Blood Cells	$x10^9$ cells/L	<3.0	>16
Neutrophils	$x10^9$ cells/L	<1.5	>13.5
Lymphocytes	$x10^9$ cells/L	<0.8	>12
Monocytes	$x10^9$ cells/L	N/A	>2.5
Eosinophils	$x10^9$ cells/L	N/A	>1.6
Basophils	$x10^9$ cells/L	N/A	>1.6
Hemoglobin for females for males	g/L	≤ 95 ≤ 115	≥175 ≥190
Hematocrit for females for males	%	≤ 32 ≤ 37	≥54 ≥60
Red Blood Cells (RBC)	$x10^{12}$ cells/L	≤ 3.5	≥6.4
Platelet count	$x10^9$ cells/L	≤ 75	≥700
Chemistry			
Sodium	mmol/L	≤ 126	≥ 156
Potassium	mmol/L	≤ 3	≥ 6
Chloride	mmol/L	≤ 90	≥ 118
Bicarbonate	mmol/L	≤ 16	≥ 35

Calcium	mmol/L	≤ 2	≥ 3
Phosphorous	mmol/L	≤ 0.5491	≥ 1.7119
Aspartate aminotransferase (AST)	IU/L	N/A	≥ 3x ULN
Alanine Aminotransferase (ALT)	IU/L	N/A	≥ 3x ULN
Alkaline phosphatase	IU/L	N/A	≥ 3x ULN
Creatinine	umol/L	N/A	≥ 1.5x ULN
Total Bilirubin	umol/L	N/A	≥ 1.5x ULN
Total Protein	g/L	≤ 45	≥ 100
Albumin	g/L	≤ 25	N/A
Uric Acid for females for males	umol/L	N/A N/A	≥ 501.5 ≥ 619.5
Glucose (non-fasting)	mmol/L	≤ 2.2	≥ 13.75

5.8.5. Vital Sign Measurements

Vital signs are collected at all study visits except that height is obtained at Baseline visit only. The analysis of vital signs will focus on the incidence of clinically relevant abnormalities from Day 1/Baseline to the Follow-up visit (EOS visit (Week 84 or earlier for early termination subjects) for those who do not enroll in Part 2, or Part 2 Day 1 visit for those who enroll in Part 2 of the study). The criteria for clinically relevant post-baseline abnormalities are given in **Table 3**.

Table 3: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C or an increase from baseline of at least 1°C
Pulse	>100 beats per minute (bpm) or an increase from baseline of >30 bpm <40 bpm or a decrease from baseline of >20 bpm
Systolic Blood Pressure	>160 mmHg or an increase from baseline of >40 mmHg <90 mmHg or a decrease from baseline of >30 mmHg
Diastolic Blood Pressure	>100 mmHg or an increase from baseline of >30 mmHg <45 mmHg or a decrease from baseline of >20 mmHg

A summary table for subjects with any clinically relevant post-baseline abnormalities will be provided. In the summary table, entries are numbers of subjects with an abnormality divided by number of subjects evaluated followed by corresponding percentages. Number evaluated is the number of subjects who had a baseline assessment and at least one post-baseline assessment for that vital sign.

The number and percentage of subjects with post-baseline weight change of greater than 7% from baseline will be summarized by treatment group and visit. A subject listing of post-baseline weight change of greater than 7% from baseline will be presented.

For temperature, pulse, systolic blood pressure, diastolic blood pressure, respiratory rate and weight, actual values and changes from baseline will be summarized using descriptive statistics by treatment group and visit. Box and whisker plots displaying values and changes from baseline by visit will also be presented.

A subject listing will be presented for subjects with any post-baseline clinically relevant abnormalities in vital signs. In this listing, each subject's complete vital sign values from screening to last study visit will be listed with abnormalities labeled.

5.8.6. Physical Examination

Physical examination is performed every 12 weeks from Week 0 to Week 72 and at unscheduled visits. The result collected on CRF at scheduled visits will be listed as performed or not performed, and abnormality will be reported as AE.

5.8.7. 12-lead ECG Readings

ECG is assessed at Screening, Week 24, Week 48, Week 72, ET, and Follow-up visit (EOS visit (Week 84 or earlier for early termination subjects) for those who do not enroll in Part 2, or Part 2 Day 1 visit for those who enroll in Part 2 of the study). The ECG result is classified as "normal", "abnormal", "abnormal, not adverse event", or "abnormal, adverse event".

Status change in ECG from screening at Week 24, Week 48, Week 72, and Follow-up visit will be summarized using shift tables. The number and percent of subjects with shifts from normal to abnormal values ("abnormal, not adverse event", or "abnormal, adverse event") will be summarized by treatment group.

A listing of details for abnormal ECG findings will also be presented.

5.8.8. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is an assessment that evaluates suicidal ideation and behavior. C-SSRS measurements are collected with respect to "Lifetime: time he/she felt most suicidal" at baseline, and with respect to "Since last visit" at Week 24, 48, 72, ET and Follow-up Visit.

There are 11 common "Yes/No" questions at baseline and post-baseline visits. Five questions on *suicidal ideation* and five questions on *suicidal behavior* are re-ordered and follow increasing severity order respectively as shown in **Table 4**; another question on *self-injurious behavior without suicidal intent* is listed separately. In particular, only subjects who answered "Yes" to question 2 will proceed to question 3, 4 and 5. Thus, for any subjects who answered "No" to

question 2, an answer "No" will also be assumed to question 3, 4, and 5. An additional "Yes/No" question is used to record if subject had committed suicide in post-baseline visits.

Table 4: C-SSRS re-ordered questions

Suicidal Ideation	
Question 1	Wish to be dead
Question 2	Non-specific active suicidal thoughts
Question 3	Active suicidal ideation with any methods (not plan) without intent to act
Question 4	Active suicidal ideation with some intent to act, without specific plan
Question 5	Active suicidal ideation with specific plan and intent
Suicidal Behavior	
Question 6	Preparatory acts or behavior
Question 7	Aborted attempt
Question 8	Interrupted attempt
Question 9	Actual attempt
Question 10	Suicidal behavior
Question 11 (post-baseline visit only)	Suicide
Self-Injurious Behavior without Suicidal Intent	
Question 12	Self-injurious behavior without suicidal intent

A subject is considered to have *suicidal ideation* at the period of interest if a "Yes" is answered to any of the five suicidal ideation questions (Question 1-5). A subject is considered to have *suicidal behavior* at the period of interest if a "Yes" is answered to any of the five suicidal behavior questions (Question 6-10) at baseline or a "Yes" is answered to any of the six suicidal behavior questions (Question 6-11) at post-baseline visit.

A subject's *Suicidal Ideation Score* is defined as the maximal suicidal ideation question number (maximal of 1-5) with an answer "Yes" per visit. The score is defined as 0 if the subject answered "No" to all 5 Suicidal Ideation questions at that visit. A subject is considered to have treatment-emergent suicidal ideation if the subject had either new or worsening suicidal ideation. A subject is considered to have new suicidal ideation if the subject's Suicidal Ideation Score

increased at any post-baseline visit compared to a score 0 at baseline. A subject is considered to have worsening suicidal ideation if the subject's Suicidal Ideation Score increased at any post-baseline visit compared to a positive score at baseline.

A subject is considered to have treatment-emergent suicidal behavior if the subject answered "Yes" to any suicidal behavior questions at any post-baseline visit while answered "No" to all suicidal behavior questions at baseline.

The following analyses on C-SSRS measurements will be conducted:

- Descriptive summary of subjects who answered "Yes" to any question 1-12 as well as subjects who had suicidal ideation or suicidal behavior at baseline and at any post-baseline visit. The denominator for baseline summary is the number of subjects who were dosed and had baseline assessment; the denominator for post-baseline summary is the number of subjects who were dosed and had at least one post-baseline assessment for each question.
- Descriptive summary of subjects who had treatment-emergent suicidal ideation, subjects who had new suicidal ideation as well as subjects who had worsening suicidal ideation. The denominator is the number of dosed subjects with both baseline and at least one post-baseline suicidal ideation assessment.
- Descriptive summary of subjects who had treatment-emergent suicidal behavior. The denominator is the number of subjects who answered "No" to all suicidal behavior questions at baseline and had at least one post-baseline suicidal behavior assessment.

Listing of subjects having treatment-emergent suicidal ideation will be provided. Subjects who had new suicidal ideation and subjects who had worsening suicidal ideation will be flagged. The listing will display both baseline and post-baseline Suicidal Ideation Scores for each subject. Listing of subjects having treatment-emergent suicidal behavior will also be provided.

5.8.9. MS Signs and Symptoms

Typical MS signs and symptoms are evaluated at screening, baseline and every 12 weeks until Week 72, and at unscheduled visit, ET visit, Follow-up visit. MS signs and symptoms are listed in 7 classes as well as sensory disturbances and motor disturbances. Number and percentage of subjects having each listed MS signs and symptoms at each visit will be displayed by treatment groups.

[redacted]

[redacted]

5.10. Immunogenicity (Anti-BIIB033 Antibodies)

Immunogenicity may affect PK and the blood levels could be lower in those study subjects who develop anti-drug antibodies. The anti-BIIB033 antibody presence will be presented in subject listings as mentioned in Section 5.9.2. Additional analysis may be conducted and will be included in a separated report from CPP.

5.11. Statistical Considerations for Interim Analysis

5.11.1. Futility Criteria

The futility criteria are determined by balancing and controlling the false negative rate (FNR) and false positive rate (FPR), and considering the overall trend of the IA data. The proposed futility threshold is the observed treatment difference in ORS at Week 36 $\leq$0.3, i.e. the futility threshold is met if the observed treatment effect (treatment difference of ORS at week 36 in BIIB033 compare to placebo) is not large than 0.3. The minimum observed treatment difference is based on statistical simulation, with assumption of true treatment difference of 0.5 which is

based on the data from SYNERGY study while controlling FNR at 10% and FPR at 3%. The futility criteria take into account of the observed treatment effect set by the futility threshold, as well as the overall trend and totality of data at the IA.

5.11.2. Interim Analysis

Main analysis for the primary and secondary endpoints will be conducted for interim analysis, with endpoints defined over 36 weeks (based on the data maturity at the planned IA) instead of over 72 weeks that is designed for the PA, and the analysis methods applied are as described in Section 5.7.2.1, Section 5.7.3.1 and Section 5.7.3.4. The futility threshold will be based on the LS adjusted means of treatment difference between BIIB033 vs. Placebo at week 36 from MMRM model. Plot of the LS adjusted mean of each treatment group with 95% CI at each visit will be provided to assess the ORS trend over time. The revised version of the supportive analysis in secondary endpoints considering tentative improvement assumed to be confirmed if no visits after Week 36 (Section 5.7.3.2 and Section 5.7.3.5) will also be performed to support the IA data interpretation.

5.11.3. Regular Safety Analysis by DMC

Safety data will be reviewed on an ongoing basis by the Data Monitoring Committee (DMC) during Part 1. Safety data are reviewed on a quarterly basis by DMC.

All adverse events (AEs) and serious adverse events (SAEs), MS relapse, clinical laboratory abnormalities, vital sign measurements, physical examination findings, 12-lead ECG readings, MS signs and symptoms, body weight and Columbia Suicide Severity Rating Scale (C-SSRS) will be evaluated for safety at interim analysis.

[redacted]

6. Changes from Protocol-Specified Analyses

COVID-19 Related Analyses

In 2020 there is a worldwide outbreak of respiratory disease named as “Coronavirus Disease 2019” (COVID-19). It has been recognized that this COVID-19 public health emergency may impact the conduct of clinical trials of medical products and the challenges caused by the COVID-19 pandemic may lead to difficulties in meeting protocol-specified procedures,

including administering the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing (FDA 2020 and EMA 2020).

For this study 215MS202, no subject in the study Part 1 had COVID-19 infection. Majority of the study Part 1 conduct and data collection have completed by the time of the COVID-19 outbreak. No subject visit from Day 1 to Week 72 is impacted by the COVID-19 pandemic, however, there are small number of subjects whose Week 84/EOS or Part 2 Day 1 visits are impacted. There were also challenges to conduct on-site monitoring visits and thereof result in some study data pending source data verification (SDV).

Therefore, the following analyses are added to assess the impact of COVID-19 pandemic. Supportive analyses on CDI and CDW MCEs are added by including tentative events that were unable to be confirmed due to missing Week 84/EOS or Part 2 Day 1 visits impacted by COVID-19 pandemic. Summaries of study subjects with early withdrawal, protocol deviation, missing or out-of-window key disability assessments due to COVID-19 pandemic are to be provided. The incomplete SDV on dosing information and key disability assessments due to the pandemic will also be summarized by visit.

[redacted]

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

Document Format Change

This SAP document is reformatted to follow the suggested content and structure in the Biogen Statistical Analysis Plan Template version 1.0 released in January 2020.

Updates Following Protocol Amendment

In this study 215MS202 protocol version 3, an open-label extension, i.e., Study Part 2, is added. Accordingly, in this version of the SAP, amendments have been made to reflect this change in study design, with corresponding updates in study procedures and data collection, as well as planned analyses.

Additional Endpoints and Analyses about MCEs of CDI and CDW

As discussed in Section 6, additional MCEs of CDI and CDW based on alternative definitions are added for supportive analyses to aid the interpretation of treatment effect on clinical disability.

Changes in Planned Analysis Methods

A few changes are made to the planned analysis methods to best suit the characteristics of the data to be analyzed, as well as to focus on the most relevant analyses addressing the trial objectives and scientific questions of interest. These changes include the following. For analyses related to brain imaging lesion count data over time, MMRM is replaced by Negative Binomial regression. For analyses related to brain imaging lesion volume over time, MMRM is replaced by Van Elteren's test. GEE and WLW approaches for supportive analyses on proportion and time to CDI are removed. Supportive analyses using multiple imputation for ORS over 72 weeks are added. Supportive analyses are added on CDI by removing data after DMT switch. The definition of per-protocol population is also updated by adding the consideration of some major protocol deviations that could potentially impact efficacy results.

COVID-19 Related Analyses

As discussed in Section 6, additional analyses are added in the SAP to assess impact of the COVID-19 pandemic and ensure the robustness of the primary analysis results.

8. References

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[3] FDA Guidance for Industry: Statistical considerations for clinical trials during the COVID-19 public health emergency (2020)

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[redacted]

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APPENDICES

Appendix I Visit Window Mapping

Table 5: Visit Windows

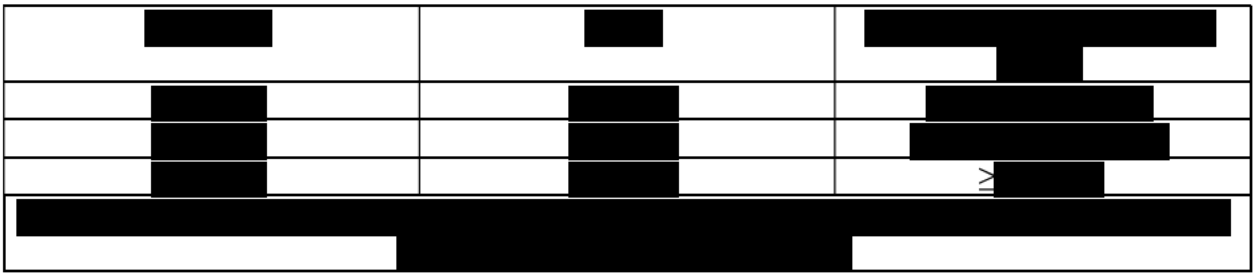
EDSS, T25FW, 9HPT, PASAT-3, [redacted], SDMT, [redacted], MS signs and symptoms, Physical Exam, Weight		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Baseline	Day 1	Day 1 being the first day of dosing
Week 12	Day 85	Day 2 to 127
Week 24	Day 169	Day 128 to Day 211
Week 36	Day 253	Day 212 to Day 295
Week 48	Day 337	Day 296 to Day 379
Week 60	Day 421	Day 380 to Day 463
Week 72	Day 505	Day 464 to Day 547
Week 84	Day 589	≥Day 548
NOTE: These assessments are measured every 12 weeks in Part 1.		

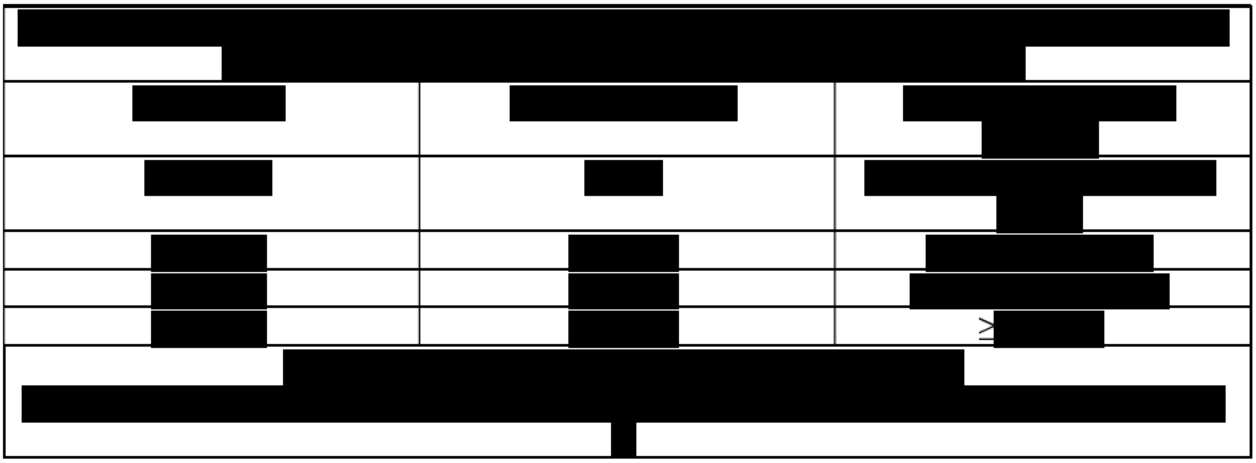
12-Lead ECG		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Baseline	Day 1	Day 1 being the first day of dosing
Week 24	Day 169	Day 2 to Day 253
Week 48	Day 337	Day 254 to Day 421
Week 72	Day 505	Day 422 to Day 547
Week 84	Day 589	≥Day 548
NOTE: These assessments are measured every 24 weeks in Part 1.		

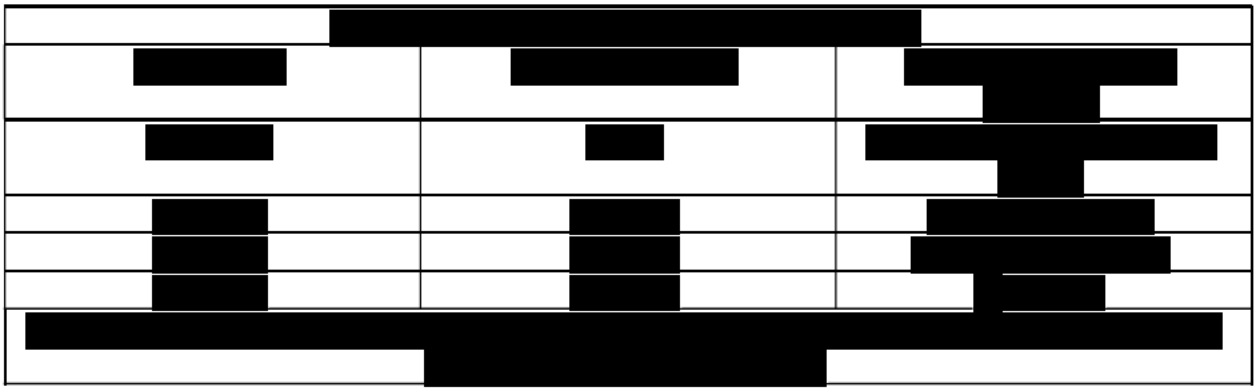
Vital Signs		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Baseline	Day 1	Day 1 being the first day of dosing
Week 4	Day 29	Day 2 to 43
Week 8	Day 57	Day 44 to 71
Week 12	Day 85	Day 72 to 99
Week 16	Day 113	Day 100 to 127

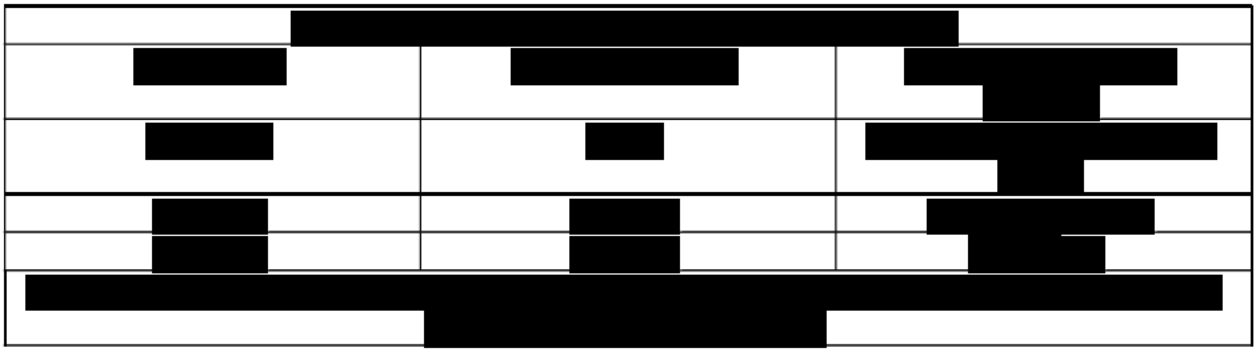
Week 20	Day 141	Day 128 to 155
Week 24	Day 169	Day 156 to Day 183
Week 28	Day 197	Day 184 to Day 211
Week 32	Day 225	Day 212 to Day 239
Week 36	Day 253	Day 240 to Day 267
Week 40	Day 281	Day 268 to Day 295
Week 44	Day 309	Day 296 to Day 323
Week 48	Day 337	Day 324 to Day 351
Week 52	Day 365	Day 352 to Day 379
Week 56	Day 393	Day 380 to Day 407
Week 60	Day 421	Day 408 to Day 435
Week 64	Day 449	Day 436 to Day 463
Week 68	Day 477	Day 464 to Day 491
Week 72	Day 505	Day 492 to Day 547
Week 84	Day 589	≥Day 548
NOTE: These assessments are measured every 4 weeks in Part 1.		

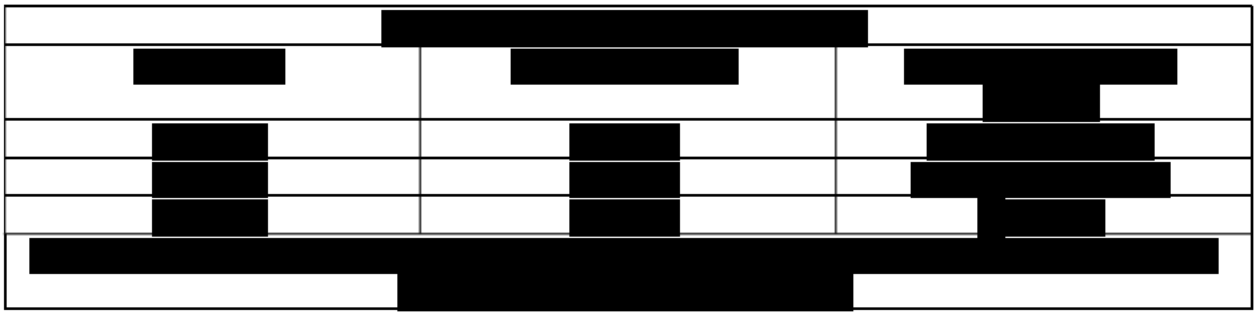
Hematology, Blood Chemistry and Urinalysis		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Baseline	Day 1	Day 1 being the first day of dosing
Week 4	Day 29	Day 2 to 43
Week 8	Day 57	Day 44 to 71
Week 12	Day 85	Day 72 to 99
Week 16	Day 113	Day 100 to 127
Week 20	Day 141	Day 128 to 155
Week 24	Day 169	Day 156 to Day 211
Week 36	Day 253	Day 212 to Day 295
Week 48	Day 337	Day 296 to Day 379
Week 60	Day 421	Day 380 to Day 463
Week 72	Day 505	Day 464 to Day 547
Week 84	Day 589	≥Day 548
NOTE: These assessments are measured every 4 weeks before Week 24, and then every 12 weeks afterwards in Part 1.		











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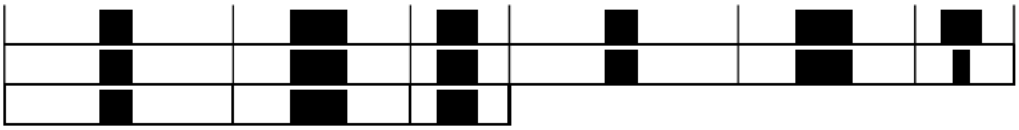

Appendix IV Study Activities

Part 1 – Schedule of Activities

Table 7: Part 1 – Study Activities (Screening to Week 52)

Tests and Assessments[1]	**Pretreatment**	**Treatment Period**													
	Screening	**Baseline**	**Visit Every 4 Weeks (±5 Days)**												
Study Week (W) **Day (D)**	**W -4 to D -1**	**W0** **D1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Informed consent	X														
Eligibility criteria check	X	X													
Randomization		X													
Medical history and prior MS treatment	X	X													
Hepatitis B and C screen	X														
Physical examination	X	X[2]			X			X			X			X	
[redacted]															
T25FW, 9HPT-D, 9HPT-ND[4]	X	X			X			X			X			X	
[redacted]															
SDMT	X	X			X			X			X			X	
EDSS[5]	X	X			X			X			X			X	
PASAT-3	X	X			X			X			X			X	
MS signs and symptoms	X	X[2]			X			X			X			X	
Weight, height[6]	X	X[2]			X			X			X			X	
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X							X						X	
Hematology[8]	X	X[2]	X	X	X	X	X	X			X			X	
Blood chemistry	X	X[2]	X	X	X	X	X	X			X			X	

Tests and Assessments[1]	**Pretreatment**	**Treatment Period**													
	Screening	**Baseline**	**Visit Every 4 Weeks (±5 Days)**												
Study Week (W) **Day (D)**	**W –4 to D -1**	**W0** **D1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Urinalysis	X	X[2]	X	X	X	X	X	X			X			X	
Serum FSH[9]	X														
Serum pregnancy test[10]	X														
Urine pregnancy test[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															
Anti-BIIB033 Ab[13]		X	X		X			X						X	
[redacted]															
Practice tests[16]	X														
[redacted]															
BIIB033 or placebo IV infusion[19]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS		X						X						X	
AEs			----------AE monitoring from study treatment dosing through to EOS----------												
SAEs	----------SAE monitoring from signing of ICF through to EOS----------														
Concomitant therapy	----------Concomitant therapy monitoring from signing of ICF through to EOS----------														

9HPT-D,-ND=9-Hole Peg Test (dominant hand, nondominant hand); Ab=antibody; AE=adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; [redacted] ECG=electrocardiogram; eCRF=electronic case report form; EDSS=Expanded Disability Status Scale; EMS=Early Multiple Sclerosis; EOS=End of Study; ET=Early Termination; [redacted]; ICF=Informed Consent Form; IV=intravenous; [redacted] MS=multiple sclerosis; [redacted] PASAT-3=3-Second Paced Auditory Serial Addition Test; [redacted] PT=prothrombin time; PTT=partial thromboplastin time; [redacted] SAE=serious adverse event; SDMT=Symbol-Digit Modalities Test; T25FW=Timed 25-Foot Walk.

Note: See **Table 8** for other study visits, including Unscheduled Visit for Relapse Assessment and ET and EOS Visits.

[1] Tests and assessments should be performed in the order listed, where possible. It is not required that all Screening tests and assessments be completed during 1 pretreatment visit.
[2] If a Screening test is performed within 7 days of Day 1/Baseline, the assessments do not need to be repeated at Day 1/Baseline.
[redacted]
[4] At each visit, T25FW, 9HPT-D, and 9HPT-ND must be tested twice each. Tests should be performed in the following order where possible: T25FW, 9HPT-D, 9HPT-ND, [redacted], and SDMT before EDSS.
[5] EDSS score is required to be stable between Screening and Day 1/Baseline Visits. Refer to the Study Reference Guide for additional instructions.
[6] Height will be measured at Screening only.
[7] Include temperature, blood pressure, pulse rate, and respiratory rate (after being seated for at least 5 minutes).
[8] PT, PTT, and platelets will also be measured for all subjects at Screening.
[9] Required for postmenopausal female subjects only.
[10] For females of child-bearing potential. Results must be known prior to Day 1/Baseline.
[11] For females of child-bearing potential. Results must be known prior to each study treatment administration.
[redacted]
[13] Predose samples (sample should be taken within 1 hour prior to study treatment dosing if possible) on Day 1/Baseline and at Weeks 4,12, 24, 48, and 72 and EOS/ET. Exact collection times will be recorded in the eCRF.
[redacted]
[16] Subjects should perform a separate practice test for T25FW, 9HPT-D, 9HPT-ND, and PASAT-3 at their Screening Visit. T25FW, 9HPT-D, and 9HPT-ND should be performed twice. The Screening and practice tests on these measurements should be separated by at least 1 hour. The Screening and Baseline tests on these measurements should be separated by at least 5 days.
[redacted]
[19] For subjects on natalizumab (Tysabri), natalizumab infusions and study treatment infusions may be on the same day; however, natalizumab should be administered prior to study treatment (BIIB033 or placebo) if given on that same day, with a minimum 1-hour interval between infusions. If any infusion reaction occurs with natalizumab, the infusion of BIIB033 should not be administered on that same day.

Table 8: Part 1 – Study Activities (Week 56 to Week 84)

	Treatment Period							Follow-Up
Tests and Assessments[1]	**Visit Every 4 Weeks (±5 Days)**					**Unscheduled Visit for Relapse Assessment[2] (Within 5 Days of the Onset)**	**ET[3]**	**EOS[4]**
Study Week (W)	**W56**	**W60**	**W64**	**W68**	**W72[5]**			**W84 ± 10 days**
Informed consent for Part 2[6]					X			
Eligibility criteria check for Part 2					X			
Physical examination		X			X	X	X	X
T25FW, 9HPT-D, 9HPT-ND[8]		X			X	X[9]	X	X
SDMT		X			X	X[9]	X	X
EDSS		X			X	X[9]	X	X
PASAT-3		X			X	X[9]	X	X
MS signs and symptoms		X			X	X	X	X
Weight		X			X	X	X	X
Vital signs[10]	X	X	X	X	X	X	X	X
12-Lead ECG					X		X	X
Hematology		X			X	X[11]	X	X
Blood chemistry		X			X	X[11]	X	X
Urinalysis		X			X	X[11]	X	X
Urine pregnancy test[12]	X	X	X	X	X		X	X

	Treatment Period							Follow-Up
Tests and Assessments[1]	**Visit Every 4 Weeks (±5 Days)**					**Unscheduled Visit for Relapse Assessment**[2] **(Within 5 Days of the Onset)**	**ET**[3]	**EOS**[4]
Study Week (W)	**W56**	**W60**	**W64**	**W68**	**W72**[5]			**W84 ± 10 days**
[redacted]								
Anti-BIIB033 Ab[14]					X		X	X
[redacted]								
BIIB033 or placebo IV infusion[19]	X	X	X	X	X			
C-SSRS					X		X	X
AEs	----------AE monitoring from study treatment dosing through to EOS----------							
SAEs	----------SAE monitoring from signing of ICF through to EOS----------							
Concomitant therapy	----------Concomitant therapy monitoring from signing of ICF through to EOS----------							

9HPT-D, -ND=9-Hole Peg Test (dominant hand, nondominant hand); Ab=antibody; AE=adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; eCRF=electronic case report form; EDSS=Expanded Disability Status Scale; EMS=Early Multiple Sclerosis; EOS=End of Study; ET=Early Termination; [redacted]; ICF=Informed Consent Form; IV=intravenous; [redacted] PASAT-3=3-Second Paced Auditory Serial Addition Test; [redacted] SAE=serious adverse event; SDMT=Symbol-Digit Modalities Test; [redacted] T25FW=Timed 25-Foot Walk.

1 Tests and assessments should be performed in the order listed where possible.

2 If a suspected MS relapse occurs during the study, the subject should return to the study site within 5 days after onset of the event for evaluation. Unscheduled visits to be determined at the discretion of the Investigator for nonsuspected relapses.

3 In the event that a subject withdraws from the study prematurely, an ET visit should be performed as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS study visit 12 weeks (±10 days) after the final dose of study treatment; all EOS assessments listed in the study schedule should be performed at this EOS visit.

4 For subjects not participating in Part 2, EOS visit occurs at 12 weeks (±10 days) after administration of the last dose of study treatment.

5 For subjects participating in Part 2, Week 72 will be the combined final Part 1 Visit and the Part 2 Screening Visit (see **Part 2 – Schedule of Activities Table 9**).

6 Informed consent for the optional substudy is obtained at Week 72 for subjects participating in Part 2.

[redacted]

8 At each visit, T25FW, 9HPT-D, and 9HPT-ND must be tested twice each. Tests should be performed in the following order where possible: T25FW, 9HPT-D, 9HPT-ND, [redacted], and SDMT before EDSS

9 EDSS, T25FW, 9HPT, LCVA, SDMT, and PASAT-3 should only be assessed at an unscheduled visit if relapse is suspected. Refer to the Study Reference Guide for additional instructions.

10 Include temperature, blood pressure, pulse rate, and respiratory rate (after being seated for at least 5 minutes).

11 To be performed only at the discretion of the treating physician if infection or metabolic disturbance is suspected to be contributing to the unscheduled visit.

12 For females of child-bearing potential. Results must be known prior to each study treatment administration.

[redacted]

14 Predose samples (sample should be taken within 1 hour prior to study treatment dosing if possible) on Day 1/Baseline and at Weeks 4,12, 24, 48, and 72 and EOS/ET. Exact collection times will be recorded in the eCRF.

[redacted] be used for efficacy analysis. If a subject's study [redacted]

19 For subjects on natalizumab (Tysabri), natalizumab infusions and study treatment infusions may be on the same day; however, natalizumab should be administered prior to study treatment (BIIB033 or placebo) if given on that same day, with a minimum 1-hour interval between infusions. If any infusion reaction occurs with natalizumab, the infusion of BIIB033 should not be administered on that same day.

Part 2 – Schedule of Activities

Table 9: Part 2 – Study Activities (Screening to Week 52)

Tests and Assessments[1]		**Treatment Period**													
	Screening[2]	**Part 2/Day 1**[3]	**Visit Every 4 Weeks (±5 Days)**												
Study Week (W) Day (D)	**W -4 to D -1**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Informed consent[4]	X	X													
Eligibility criteria check	X	X													
Physical examination	X	X						X						X	
[redacted]															
T25FW, 9HPT-D, 9HPT-ND[6]		X						X						X	
[redacted]															
SDMT		X						X						X	
[redacted]															
EDSS		X						X						X	
PASAT-3		X						X						X	
MS signs and symptoms	X	X						X						X	
Weight, height[8]	X	X			X			X			X			X	
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X			X			X			X			X	
Hematology[10]	X	X			X			X			X			X	
Blood chemistry	X	X			X			X			X			X	
Urinalysis	X	X			X			X			X			X	
Urine pregnancy test[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															

Tests and Assessments[1]		**Treatment Period**													
	Screening[2]	**Part 2/Day 1**[3]	**Visit Every 4 Weeks (±5 Days)**												
Study Week (W) Day (D)	**W -4 to D -1**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Blood Sample for Anti-BIIB033 Ab[12]		X						X						X	
Blood sample for lipid profile and thyroid tests		X						X						X	
[redacted]															
BIIB033 IV infusion[18]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X						X						X	
[redacted]															
AEs	←----------AE monitoring from signing of the ICF through to EOS----------→														
SAEs	←----------SAE monitoring from signing of ICF through to EOS----------→														
Concomitant therapy	←----------Concomitant therapy monitoring from signing of ICF through to EOS----------→														

[redacted]; 9HPT-D,-ND=9-Hole Peg Test (dominant hand, nondominant hand); Ab=antibody; [redacted]; AE=adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; D = Day; [redacted]; ECG=electrocardiogram; eCRF=electronic case report form; EDSS=Expanded Disability Status Scale; EMS=Early Multiple Sclerosis; EOS=End of Study; ET=Early Termination; [redacted]; ICF=Informed Consent Form; IV=intravenous; [redacted]; MS=multiple sclerosis; [redacted]; PASAT-3=3-Second Paced Auditory Serial Addition Test: [redacted]; PT=prothrombin time; PTT=partial thromboplastin time; [redacted]; SAE=serious adverse event; SDMT=Symbol-Digit Modalities Test; T25FW=Timed 25-Foot Walk; W = Week

[1] Test and assessment should be performed in the order listed where possible.

[2] Screening Visit should be performed as part of Part 1/Week 72 Visit. In case the Part 2 Screening Visit is unable to be performed at Part 1/Week 72, a separate Screening Visit may occur within 4 weeks of Part 2/Day 1. Any test/assessment done within 28 days prior to Part 2/Day 1 will be used for screening for Part 2 and does not need to be repeated.

[3] When possible, the Part 2/Day 1 should be performed 4 weeks from the Part 1/Week 72 Visit. If not possible in 4 weeks, the maximum window is 12 weeks from Part 1/Week 72, and the patients should roll over into Part 2 as soon as possible within weeks 4 to 12.

[4] Informed consent for the optional substudy should also be obtained on Part 2/Day 1 before the substudy procedures.

[6] At each visit, T25FW, 9HPT-D, and 9HPT-ND must be tested twice each. Tests should be performed in the following order where possible: T25FW, 9HPT-D, 9HPT ND, SDMT, 6MWT, and then EDSS.

[8] Height at Part 2/Day 1 only.

[9] Includes temperature, blood pressure, pulse rate, and respiratory rate (after being seated for at least 5 minutes).

[10] PT, PTT, and platelets will also be measured for all subjects on Part 2/Day 1 and at each visit when hematology is done.

[11] For females of child-bearing potential. Results must be known prior to each study treatment administration.

[17] For subjects on natalizumab (Tysabri), natalizumab infusions and study treatment infusions may be on the same day; however, natalizumab should be administered prior to BIIB033 infusion if given on that same day, with a minimum 1-hour interval between infusions. If any infusion reaction occurs with natalizumab, the infusion of BIIB033 should not be administered on that same day.

Table 10: Part 2 – Study Activities (Week 56 to Week 96)

Tests and Assessments[1]	**Treatment Period**													
	Visit Every 4 Weeks (±5 Days)											**Unscheduled Visit for Relapse Assessment**[2] **(Within 5 Days of the Onset)**	**ET**[3]	**EOS**[4]
Study Week (W)	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**			**W108± 10d**
Physical examination					X						X	X	X	X
[redacted]														
T25FW, 9HPT-D, 9HPT-ND[6]					X						X	X[6]	X	X
[redacted]														
SDMT					X						X	X[6]	X	X
[redacted]														
EDSS					X						X	X[6]	X	X
PASAT-3					X						X	X[6]	X	X
MS signs and symptoms					X						X	X	X	X
Weight					X						X	X	X	X
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG		X			X			X			X		X	X
Hematology		X			X			X			X	X[9]	X	X

Tests and Assessments[1]	**Treatment Period**													**Follow Up**
	Visit Every 4 Weeks (±5 Days)											**Unscheduled Visit for Relapse Assessment**[2] **(Within 5 Days of the Onset)**	**ET**[3]	**EOS**[4]
Study Week (W)	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**			**W108± 10d**
Blood chemistry		X			X			X			X	X[10]	X	X
Urinalysis		X			X			X			X	X[11]	X	X
Urine pregnancy test[12]	X	X	X	X	X	X	X	X	X	X	X		X	X
[redacted]														
Blood sample for Anti-BIIB033 Ab[11]					X						X		X	X
Blood sample for lipid profile and thyroid tests					X						X			
[redacted]														

Tests and Assessments[1]	**Treatment Period**													**Follow Up**
	Visit Every 4 Weeks (±5 Days)											**Unscheduled Visit for Relapse Assessment**[2] **(Within 5 Days of the Onset)**	**ET**[3]	**EOS**[4]
Study Week (W)	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**			**W108± 10d**
[redacted]														
BIIB033 IV infusion[16]	X	X	X	X	X	X	X	X	X	X	X			
C-SSRS					X[17]						X		X	X
[redacted]														
AEs	←----------AE monitoring from signing of Part 2 ICF through to EOS----------→													
SAEs	←----------SAE monitoring from signing of Part 2 ICF through to EOS----------→													
Concomitant therapy	←----------Concomitant therapy monitoring from signing of Part 2 ICF through to EOS----------→													

[redacted]; 9HPT-D, -ND=9-Hole Peg Test (dominant hand, nondominant hand); Ab=antibody; [redacted]; AE=adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; eCRF=electronic case report form; [redacted]; EDSS=Expanded Disability Status Scale; EMS=Early Multiple Sclerosis; EOS=End of Study; ET=Early Termination; hbA1C = glycated hemoglobin; [redacted]; ICF=Informed Consent Form; IV=intravenous; [redacted] mmEP = multi-modal evoked potential; [redacted]; PASAT-3=3-Second Paced Auditory Serial Addition Test; [redacted]; SAE=serious adverse event; SDMT=Symbol-Digit Modalities Test; T25FW=Timed 25-Foot Walk; W = Week

[1] Tests and assessments should be performed in the order listed where possible.

[2] If a suspected MS relapse occurs during the study, the subject should return to the study site within 5 days after onset of the event for evaluation. Unscheduled visits to be determined at the discretion of the Investigator for nonsuspected relapses.

[3] In the event that a subject withdraws from the study prematurely, an ET Visit should be performed as soon as possible but no later than 4 weeks after the last dose of study treatment.

[4] EOS Visit occurs at 12 weeks (±10 days) after administration of the last dose of study treatment. All EOS assessments listed in the study schedule should be performed at this EOS Visit.

[redacted]

[6] At each visit, T25FW, 9HPT-D, and 9HPT-ND must be tested twice each. Tests should be performed in the following order where possible: T25FW, 9HPT-D, 9HPT-ND, [redacted], SDMT, 6MWT, and then EDSS.

[redacted]

[8] Includes temperature, blood pressure, pulse rate, and respiratory rate (after being seated for at least 5 minutes).
[9] To be performed only at the discretion of the treating physician if infection or metabolic disturbance is suspected to be contributing to the unscheduled visit.
[10] For females of child-bearing potential. Results must be known prior to each study treatment administration.
[11] The period between predose sample collection and administering of the study treatment should not exceed 24 hours, and the exact time and date at which the sample was collected should be recorded in the eCRF.

[redacted]

nt administration. A central reader will be used for efficacy analysis. If a subject's study [redacted]

[redacted]

[16] For subjects on natalizumab (Tysabri), natalizumab infusions and study treatment infusions may be on the same day; however, natalizumab should be administered prior to study treatment (BIIB033 or placebo) if given on that same day, with a minimum 1-hour interval between infusions. If any infusion reaction occurs with natalizumab, the infusion of BIIB033 should not be administered on that same day.

[redacted]

STATISTICAL ANALYSIS PLAN

PART 2

Version No.: 1.0

Date: 23 April 2021

Author: [redacted]

Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with Optional Open-Label Extension in Subjects With Relapsing Multiple Sclerosis to Evaluate the Efficacy and Safety of BIIB033 as an Add-On Therapy to Anti-Inflammatory Disease-Modifying Therapies

Name of Study Treatment: BIIB033

Protocol No.: 215MS202

Study Phase: Phase II

APPROVAL

This document has been reviewed and approved by:		
[redacted]	DocuSigned by: [redacted]	23-Apr-2021
SMT Statistician	Signature	Date
[redacted]	DocuSigned by: [redacted]	23-Apr-2021
Program Statistician	Signature	Date
[redacted]	DocuSigned by: [redacted]	23-Apr-2021
Study Medical Lead	Signature	Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
Final version 1.0	7-April-2021	Final version 1.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
[redacted]	[redacted]
9HPT-D, ND	9-Hole Peg Test (dominant hand, nondominant hand)
ADL	Activities of Daily Living-Cognitive and Instrumental
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamate pyruvate transaminase
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
CBH	chronic black holes
CDI	confirmed disability improvement
CDW	confirmed disability worsening
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	data monitoring committee
DMF	dimethyl fumarate
DMT	disease-modifying therapy
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
EMS	Early Multiple Sclerosis
EOS	End of Study
ET	Early Termination
FSH	Follicle-stimulating hormone
FT4	Free thyroxine
GA	glatiramer acetate
GCP	Good Clinical Practice
[redacted]	[redacted]
GGT	Gamma glutamyl transferase
ICF	Informed Consent Form
IFN-β	interferon beta
ITT	intent-to-treat
IV	intravenous
IRT	Item Response Theory
[redacted]	[redacted]
mAb	monoclonal antibody
MCE	multicomponent endpoint

MMRM	Mixed Model for Repeated Measures
[redacted]	[redacted]
MS	multiple sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
OLE	open-label extension
ORS	Overall Response Score
PASAT-3	3-Second Paced Auditory Serial Addition Test
[redacted]	[redacted]
PK	pharmacokinetics
[redacted]	[redacted]
PT	Prothrombin time
PTT	Partial thromboplastin time
RMS	relapsing multiple sclerosis
[redacted]	[redacted]
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	Statistical analysis plan
SD	standard deviation
SDMT	Symbol-Digit Modalities Test
SDV	source data verification
[redacted]	[redacted]
SPMS	secondary progressive multiple sclerosis
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
T25FW	Timed 25-Foot Walk
T3	triiodothyronine
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
WHO	World Health Organization

1. Introduction

The purpose of this SAP is to delineate the statistical analyses as outlined in the 215MS202 Protocol V3, with details focusing on the final analysis, i.e., optional open-label extension (OLE) study Part 2 analysis. The details for study primary analysis, i.e., study Part 1 analysis are in 215MS202_SAP_v2.0.

2. Study Overview

2.1. Study Objectives and Endpoints

2.1.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety profile of BIIB033 as an add-on therapy in subjects with MS.

2.1.2. Primary Endpoint

The primary endpoint is incidence of AEs and SAEs over 96 weeks in Part 2. The endpoints for AEs and SAEs include the following:

- All treatment-emergent AEs (TEAEs).
- TEAE with severity as "moderate" or "severe".
- TEAE with severity as "severe".
- Current DMT related TEAE.
- Study treatment related TEAE.
- All SAEs.
- Current DMT related SAE.
- Study treatment related SAE.
- AE leading to discontinuation of study treatment.
- AE leading to withdrawal from study.

2.1.3. Secondary Objective

The secondary objective of this study is to investigate long-term efficacy (disability improvement) and additional safety measures of BIIB033 as an add-on therapy in subjects with MS.

2.1.4. Secondary Endpoints

The secondary endpoints are as follows:

- Overall Response Score (ORS) over 96 weeks in Part 2.
- Proportion of subjects with 24-week confirmed disability improvement (CDI) in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND (improvement in T25FW and 9HPT is defined as a ≥15% decrease from BIIB033 Treatment Baseline).

- Proportion of subjects with 24-week CDI in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, PASAT-3 (improvement in PASAT-3 is defined as a ≥15% increase from BIIB033 Treatment Baseline).
- Proportion of subjects with 24-week CDI in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND, and without confirmed disability worsening (CDW) in any of the 4 assessments during the 96 weeks of the study.
- Proportion of subjects with 24-week CDI in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, SDMT (improvement in SDMT is defined as a ≥4-point increase from BIIB033 Treatment Baseline).
- Proportion of subjects with 24-week CDI in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D and 9HPT-ND (20% thresholds for T25FW and 9HPT).
- Potentially clinically significant abnormal laboratory, ECG, vital signs, and weight values over 96 weeks in Part 2.
    - Clinical laboratory results are summarized for potentially clinically significant abnormalities, shift analyses, liver function laboratory tests, summary and listings of actual values and change from baseline. The endpoints for clinical laboratory results include the following:
        - Hematology: complete blood count with differential and platelet count, and absolute neutrophil count. Prothrombin time (PT), partial thromboplastin time (PTT) and platelets will also be measured for all subjects at screening.
        - Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), gamma glutamyl transferase (GGT), glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium and follicle-stimulating hormone (FSH: for postmenopausal female subjects only).
        - Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal).
        - Serum and urine pregnancy test (women of child-bearing potential only).
    - MS relapse.
    - ECG.
    - Vital signs. The endpoints for vital signs include the following:
        - Temperature.
        - Pulse.
        - Systolic Blood Pressure.
        - Diastolic Blood Pressure.
    - Weight values. The endpoints for weight values include the following:

  - Occurrence of a post-baseline weight change of greater than 7% from baseline.
  - Change from baseline in weight.
- Physical examination.
- MS signs and symptoms.
- C-SSRS score over 96 weeks in Part 2.

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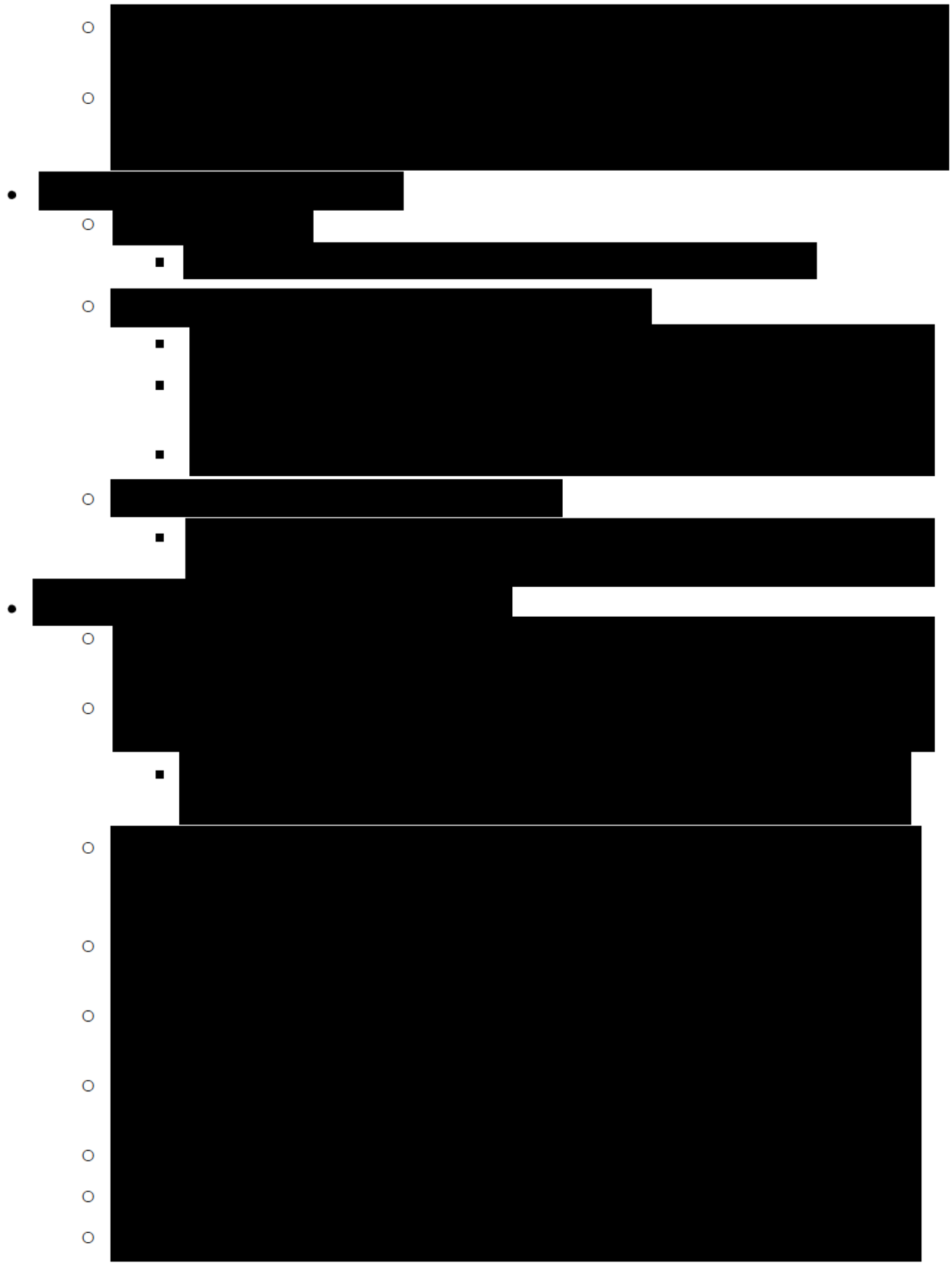

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- [redacted]

2.2. Study Design

This is a Phase 2 multicenter study conducted in 2 parts. Part 1 is a 72-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 study to evaluate the efficacy and safety of BIIB033 (750 mg infused IV every 4 weeks) as an add-on therapy to a background DMT in subjects with RMS. Part 2 is a 96-week open-label extension that will assess long-term safety and efficacy of BIIB033 administered for approximately 24 additional months.

In Part 1 of the study, approximately 240 eligible subjects will be randomized into the active treatment group (BIIB033 750 mg) or placebo in a 1:1 ratio at approximately 150 sites in approximately 25 countries. Randomization will be stratified by MS type (RRMS versus SPMS), background DMT group, [redacted].

The study treatment in Part 1 includes BIIB033 or placebo, administered once every 4 weeks by IV infusion for a total of 19 doses over 72 weeks. All enrolled subjects must have been treated for at least 24 consecutive weeks prior to enrollment on an anti-inflammatory DMT and will continue taking their DMT throughout the study. Based on the clinical judgment of the treating neurologist, subjects can switch to another marketed DMT during the study or may discontinue the DMT altogether.

Each subject in Part 1 will have a total of 21 scheduled study visits:

- Screening (pre-treatment)
- Treatment Period: 1 visit every 4 weeks between Day 1/Baseline and Week 72 (19 visits)
- Follow-up Period (Post-treatment): End of Study (EOS) Visit (Week 84) for subjects who do not participate in Part 2.

Part 1 of the study will include clinical assessments every 12 weeks. Each subject will have separate treating and examining neurologists; the roles of the treating and examining neurologist are not interchangeable even for different subjects.

In Part 2 of the study, subjects who have completed study treatment (BIIB033 or placebo) in Part 1, have consented and are eligible to participate in Part 2 of the study will be enrolled.

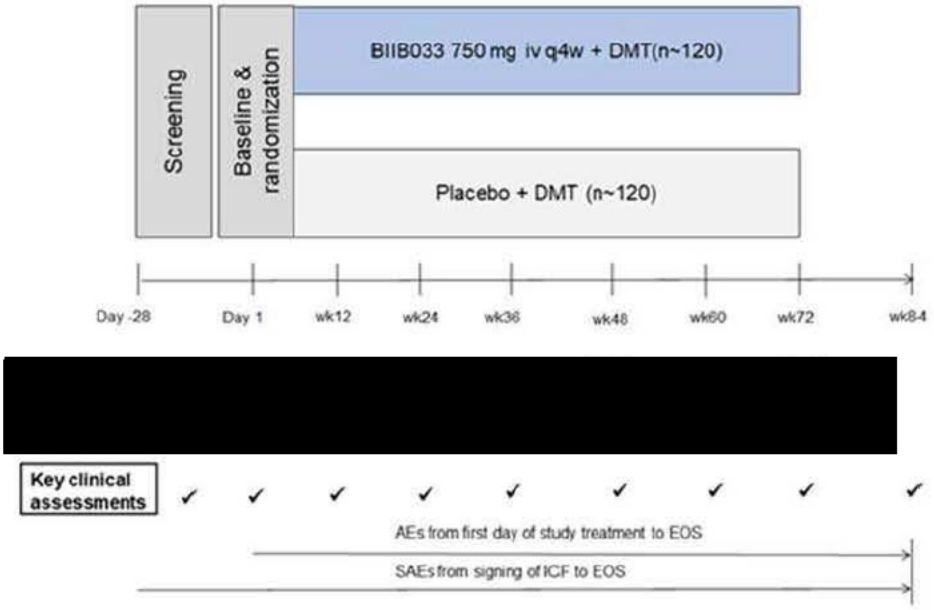
Subjects enrolled in Part 2 of the study will receive BIIB033 by IV infusion once every 4 weeks for a period of approximately 96 weeks. All subjects in Part 2 will continue the anti-inflammatory DMT used at the end of Part 1. The maximum allowed time for rollover into Part 2 of the study (Day 1) is 12 weeks after the Part 1/Week 72 Visit. Clinic visits will be conducted once every 24 weeks, [redacted]

[redacted]

Study treatment allocation in Part 1 will remain blinded for all Part 2 subjects and all site staff.

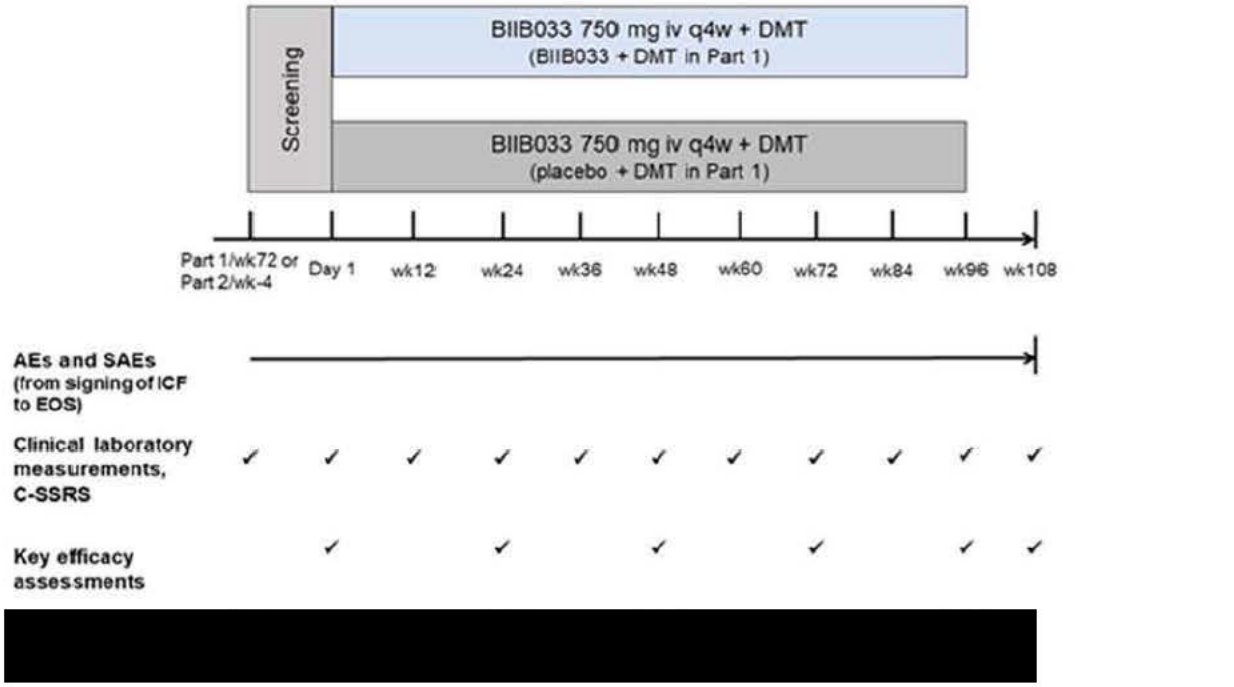
See **Figure 1** and **Figure 2** for a schematic of the study design for Part 1 and Part 2, respectively.

Figure 1: Part 1- Study Schematic



AE = adverse event; DMT=disease-modifying therapy; EOS = End of Study; ICF = informed consent form; IV=intravenous; [redacted]; n=number of patients; q4w=every 4 weeks; SAE = serious adverse event; wk = week

Figure 2: Part 2 – Study Schematic



AE = adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; DMT=disease-modifying therapy; EOS = End of Study; ICF = informed consent form; IV=intravenous; [redacted] n=number of patients; q4w=every 4 weeks; SAE = serious adverse event; wk = week

2.3. Study Duration for Subjects

The total duration of study participation in Part 1 for each subject will be up to approximately 88 weeks; this consists of a Screening Period of up to 4 weeks, a Treatment Period of 72 weeks, and a Follow-up Period of 12 weeks. Subjects enrolled in Part 2 do not need to have the 12-week follow-up (EOS) after the last dose of study treatment in Part 1; thus, the study duration in Part 1 will be approximately 76 weeks.

The total duration of study participation in Part 2 for each subject will be up to approximately 112 weeks; this consists of a Screening Period of up to 4 weeks, a Treatment Period of 96 weeks, and a Follow-up Period of 12 weeks.

The total duration for subjects who participate in both Part 1 and Part 2 will be approximately 188 weeks.

For details about Screening, Treatment Period, unscheduled visits(s) and treatment for relapse and Follow-up, please see protocol Section 7.2.

2.4. Sample Size Considerations

In Part 1, a sample size of 120 subjects per treatment group will have approximately 80% power to detect a treatment effect of 0.354 in ORS over 72 weeks comparing to placebo. This power calculation is based on a 1-sided 2-sample t-test assuming equal variance with a significance level of 0.025, an SD of 0.85, and a drop-out rate of 20%. The assumed treatment effect of 0.354 is based on the 90% one-sided lower confidence bound of the estimated treatment effect in the target population of Study 215MS201.

In Part 2, the actual sample size, [redacted] is dependent on the enrollment rate; therefore, a sample size calculation is not needed.

3. Definitions

3.1. Study Treatment

Study treatment in this SAP, unless otherwise specified, refers to the blinded treatment in Part 1 of either BIIB033 750 mg or placebo administered once every 4 weeks (Q4W) by intravenous (IV) infusion for the planned a total of 19 doses over 72 weeks in Part 1, followed by open-label treatment in Part 2 of BIIB033 750 mg administered once Q4W by IV infusion for the planned a total of 25 doses over 96 weeks in Part 2, added on to anti-inflammatory DMT. Throughout this SAP, study treatment and *study drug* are equivalent and used interchangeably.

To facilitate illustration in the analysis plan, treatment groups are listed below with short names:

Table 1: Treatment Groups

Part 1 Analyses (Interim Analysis, Primary Analysis):

Study Treatment	Short name
Blinded BIIB033 750 mg IV infusion Q4W	BIIB033 750 mg
Blinded Placebo IV infusion Q4W	Placebo

[redacted]

[redacted]

3.2. Dates and Points of Reference

Study Day 1

The *study Day 1* is defined as the date on which the first dose of study treatment is administered in Part 1.

Study Day 1 in Part 2

The *study Day 1 in Part 2* is defined as the date on which the Part 2 Day 1 dose of study treatment is administered in Part 2.

First Dose Date and Last Dose Date in Part 1

Without otherwise specified, the *first dose date* is equivalent to study Day 1 defined above, the *last dose date in Part 1* is the date of the last administration of study treatment in Part 1.

First Dose Date and Last Dose Date in Part 2

The *first dose date in Part 2* is the date on which the first dose of study treatment is administered in Part 2, the *last dose date in Part 2* is the date of the last administration of study treatment in Part 2.

End of Treatment (EOT) / Early Termination (ET)

In the event that a subject withdraws from the study prematurely, an ET visit should be performed as soon as possible but no later than 4 weeks after the last dose of study treatment. The End of Treatment eCRF page should be filled out at the ET visit. The *EOT in Part 1 date* is the End of Treatment – PART 1 date recorded on the End of Treatment eCRF page. The *EOT in Part 2 date* is the End of Treatment – PART 2 date recorded on the End of Treatment eCRF page. The *ET visit in Part 1 date* refers to the date of visit for the ET visit in Part 1. The *ET visit in Part 2 date* refers to the date of visit for the ET visit in Part 2.

End of Study (EOS)

For subjects who complete Part 1 and do not enroll into Part 2, the EOS visit is defined as the Week 84 visit; for subjects who early terminate in Part 1, the EOS visit is defined as the scheduled follow-up visit after the ET visit in Part 1, this EOS visit in Part 1 is to occur approximately 12 weeks after the last dose of study treatment in Part 1; for subjects who complete Part 1 and are enrolled into Part 2, the EOS visit in Part 2 is to occur approximately 12 weeks after the last dose of study treatment in Part 2. *The EOS date* is the End of Study date recorded on the End of Study

eCRF page. The last date in Part 1 is the latest date among all visits' end dates if a subject does not have Part 2 Day 1 visit; the last date in Part 1 is the day prior to the start date of Part 2 Day 1 visit if a subject has Part 2 Day 1 visit. The last date in Part 2 is the latest date among all Part 2 visits' end dates if a subject is enrolled in Part 2. The last date in Part 1 and Part 2 is the latest date among all visits end dates in Part 1 and Part 2.

Start Date of COVID-19 Phase

COVID-19 phase refers to the time period during which conduct of this study is impacted by COVID-19 infection or COVID-19 pandemic measures. The start date of the COVID-19 phase for this study is March 15, 2020.

COVID-19 Pandemic Measures

Refer to any action or challenges arising due to COVID-19 that may impact study conduct, including quarantines, site closures, travel limitation, interruptions to the supply chain for the investigational product, or other considerations if site personnel become infected with COVID-19.

Study Day

- For a date on or after Study Day 1

  Study Day = (Date of Interest) – (Study Day 1) + 1
- For a date before Study Day 1

  Study Day = (Date of Interest) – (Study Day 1)
- For a date on or after Study Day 1 in Part 2

  Study Day in Part 2 = (Date of Interest) – (Study Day 1 in Part 2) + 1
- For a date before Study Day 1 in Part 2

  Study Day in Part 2 = (Date of Interest) – (Study Day 1 in Part 2)

Visit Window Mapping

For data that are summarized by visit and longitudinal analysis, assessment from all scheduled visits including ET visits and EOS visits, and all unscheduled visits will be mapped to an appropriate analysis visit using a window scheme.

We intend to map Part 1 data using study Day 1 as the reference day and map Part 2 data using study Day 1 in Part 2 as reference day, except for Part 2 Screening visit which we do not map. The rationale is that according to protocol, Part 2 Day 1 in Part 2 should be performed 4 weeks from the Week 72 visit. If not possible in 4 weeks, the maximum window is 12 weeks from Week 72. The interpretation of this schedule is that the subject should perform Part 2 Day 1 visit between 4 weeks from Week 72 and 12 weeks from Week 72, with 4 weeks from Week 72 being the recommended schedule. Therefore, unlike Part 1 visits where all visits are planned to perform according to the study day using study Day 1 as the reference day, when to perform the Part 2 Day 1 visit is dependent on when the Part 1 Week 72 has been performed, instead of planning based on a fixed target day using study Day 1 as the reference day.

For Part 2 Screening visit, according to protocol, it should be performed as part of Week 72 visit but a separate Part 2 Screening visit is allowed, for subjects who have screening for Part 2 but do not rollover to Part 2, they may not have a separate Part 2 Screening visit or may have Part 2 Screening visit as a separate visit after Week 72 visit; for subjects who have screening for Part 2 and rollover to Part 2, they will have Part 2 Day 1 visit, in additional, they may not have a separate Part 2 Screening visit or may have a Part 2 Screening visit as a separate visit after Week 72 visit. We do not map Part 2 Screening visit.

The analysis visit windows are defined in **Table 5** for different endpoints.

To define the analysis visit window, the target visit day is calculated as (week number×7+1). The lower bound of the visit window is calculated as (target visit day + (target visit day of the previous visit))/2+1, except that the lower bound of the first post-baseline visit window is set as Day 2 in Part 1, and the lower bound of Part 2 Day 1 visit is set as Day -5 in Part 2 and the first post-Part 2 Day 1 visit window is set as Day 6 in Part 2. The upper bound of the visit window is calculated as (target visit day + (target visit day of the next visit))/2, except that Part 2 Day 1 visit upper bound is set as Day 5 in Part 2, and Week 84 visit and Part 2 Week 108 visit we do not set upper bound.

The lower bound and the upper bound of Part 2 Day 1 visit is set as Day -5 in Part 2 and Day 5 in Part 2 because in Part 2 Day 1 visit, there are circumstances that a few subjects whose clinical assessments could not be completed within one day so that they are performed on multiple days, but we intend to map them to Part 2 Baseline visit instead of map them to the first post-Part 2 Day 1 visit or discard them. The 5 day visit window is based on protocol allowed ±5-day visit window. Additionally, for MRI endpoints the lower bound and the upper bound of Part 2 Day 1 visit is set as Day -20 in Part 2 and Day 7 in Part 2 to allow the MRI data to be used from a subject who performed Part 2 Day 1 MRI assessment at Day -20 in Part 2 and from a subject who performed Part 2 Day 1 MRI assessment at Day 7 in Part 2.

If more than one assessment is within the same analysis visit window other than Part 1 ET, Part 2 ET, Part 1 EOS or Part 2 EOS visits, the assessment closest to the target visit day will be used for the analysis. If more than one assessment falls in the same distance from the target visit day other than Part 1 ET, Part 2 ET, Part 1 EOS or Part 2 EOS visits, the last one will be used for the analysis. If more than one assessment is on the same day other than Part 1 ET, Part 2 ET, Part 1 EOS or Part 2 EOS visits, the average value for the quantitative parameters and the worst value for the qualitative parameters will be used for the analysis.

If the Part 1 ET visit is mapped to the same analysis visit as a prior visit (either scheduled or unscheduled visit), then the Part 1 ET visit will be remapped to the next analysis visit. If Part 1 EOS visit is mapped to an analysis visit and a prior visit, e.g., Part 1 ET visit, is mapped to the same analysis visit, then Part 1 EOS visit will be remapped to the next analysis visit. For Part 1, the latest analysis visit for the Part 1 ET visit can be up to Week 72 and for Part 1 EOS visit can be up to Week 84.

If the Part 2 ET visit is mapped to the same analysis visit as a prior visit (either scheduled or unscheduled visit), then the Part 2 ET visit will be remapped to the next analysis visit. If Part 2 EOS visit is mapped to an analysis visit and a prior visit, e.g., Part 2 ET visit, is mapped to the same analysis visit, then Part 2 EOS visit will be remapped to the next analysis visit. For Part 2,

the latest analysis visit for the Part 2 ET visit can be up to Part 2 Week 96 and for the Part 2 EOS visit can be up to Part 2 Week 108.

3.3. Study Periods

Study Baseline Period and Baseline Data

The study baseline period is defined as the period from screening visit to the day prior to first administration of study treatment.

Unless stated otherwise, Study baseline data are defined as the data collected prior to the first dose, which is usually at the Day 1/Baseline visit. If there is more than one value on or before the first dose, the non-missing value closest to and prior to the first dose will be used as the baseline value.

Study Baseline Period and Baseline Data in Part 2

Study baseline period in Part 2 and baseline data in Part 2 are defined for the safety data including clinical laboratory abnormalities, vital sign measurements, physical examination, 12-lead ECG readings, C-SSRS, lipid profile, T3, FT4, TSH. The study baseline period in Part 2 is defined as the period from Day -5 in Part 2 to Day 5 in Part 2.

Study baseline data in Part 2 are defined as the data collected in the period from Day -5 in Part 2 to Day 5 in Part 2, which is usually at the Part 2 Day 1 visit. If there is more than one value in this period, the value at the Part 2 Day 1 visit will be used as the baseline value in Part 2. If there are more than one value in this period but no value at the Part 2 Day 1 visit, the value that is closest to the Part 2 Day 1 infusion date/time will be used as the baseline value in Part 2. If two values are equally close to Part 2 Day 1 infusion date/time, the value that is prior to Part 2 Day 1 infusion date/time will be used as the baseline value in Part 2.

Actual Treatment Period in Study Part 1

Actual treatment period in Part 1 of the study is defined as the period from the first infusion of study treatment to 28 days after the last infusion of study treatment in Part 1.

Actual Treatment Period in Study Part 2

Actual treatment period in Part 2 of the study is defined as the period from the first infusion of study treatment in Part 2 to 28 days after the last infusion of study treatment in Part 2.

Actual Treatment Period in Study Part 1 and Part 2

Actual treatment period in Part 1 and Part 2 of the study is defined as the period from the first infusion of study treatment to 28 days after the last infusion of study treatment in Part 2 if a subject is enrolled in to Part 2 and has received at least 1 dose in Part 2; if a subject is not enrolled into Part 2 or is enrolled into Part 2 but never receives at least 1 dose in Part 2, the Actual treatment period in Part 1 and Part 2 of the study is the period from the first infusion of study treatment to 28 days after the last infusion of study treatment in Part 1.

Treatment Emergent

An adverse event in Part 2 is defined as the event that has onset date/time on or after the Part 2 Day 1 infusion day. If a subject is not enrolled in Part 2 or is enrolled in Part 2 but never receives infusion of study treatment in Part 2, all adverse events will be considered as occurring in Part 1.

An adverse event is regarded as *treatment emergent in Part 2* of the study if the event has onset date/time on or after the first dose date/time of study treatment in Part 2, or was reported prior to the first dose in Part 2 and subsequently worsens in severity after first dose date in Part 2. Additional criteria to determine treatment emergent are described in Section 5.8.2. Unless otherwise specified, the phrase "treatment emergent" in this SAP refers to "treatment emergent in Part 2".

3.4. Key Derived Variables

3.4.1. Thresholds for Improvement and Worsening

The thresholds are defined as following:

- **Thresholds for EDSS**
  - Improvement is defined as a ≥ 1.0-point decrease in EDSS from a baseline score of ≤6.0.
  - Worsening is defined as a ≥1.0-point increase from a baseline score of ≤5.5 or a ≥0.5-point increase from a baseline score equal to 6.0.
- **15% Thresholds for T25FW, 9HPT-D and 9HPT-ND**
  - Improvement is defined as ≥15% decrease from baseline in time (seconds).
  - Worsening is defined as ≥15% increase from baseline in time (seconds).

  Throughout this SAP document, unless otherwise specified, 15% is used as the threshold for T25FW, 9HPT-D, and 9HPT-ND.
- **20% Thresholds for T25FW, 9HPT-D and 9HPT-ND**
  - Improvement is defined as ≥20% decrease from baseline in time (seconds).
  - Worsening is defined as ≥20% increase from baseline in time (seconds).

  The phrase "20% thresholds for T25FW and 9HPT" in the protocol and the SAP refers to the case that 20% being used as the threshold for T25FW, 9HPT-D, and 9HPT-ND.

3.4.2. Overall Response Score

The ORS is a multicomponent score based on 4 components: EDSS, T25FW, 9HPT-D, and 9HPT-ND. It assesses overall changes in disability over time.

At each visit, each assessment is given a score compared to baseline. Meeting or exceeding the threshold for improvement in an assessment results in a +1 score for that assessment; meeting or exceeding the threshold for worsening in an assessment results in a -1 score for that assessment; no change or subthreshold changes in an assessment results in a score of 0 for that assessment. The scores of individual assessments are summed up to provide a total ORS that ranges from +4 to -4 for each visit.

3.4.3. Definitions of Confirmed Disability Improvement and Confirmed Disability Worsening

In this SAP, the main scope is to define potential improvement (or worsening), tentative improvement (or worsening) and 12-week CDI (or CDW) for either subjects who enroll into Part 2 and have assessments of EDSS, T25FW, 9HPT-D and 9HPT-ND in both Part 1 and Part 2 or for subjects who do not enroll into Part 2 and have assessments of EDSS, T25FW, 9HPT-D and 9HPT-ND in Part 1 but do not have these four assessments in Part 2. The potential improvement (or worsening), tentative improvement (or worsening) and 12-week CDI (or CDW) definitions that are specified in Section 3.4.2. of the study Part 1 SAP are still applicable for the assessments collected in Part 1, while the definitions specified in this SAP are extensions of these original definitions, to take into account all opportunities to achieve 12-week CDI (or CDW) for these subjects enroll into Part 2, using assessments from either Part 1or Part 2.

3.4.3.1. Confirmed Disability Improvement (CDI)

CDI is assessed for each of the efficacy components (EDSS, T25FW, 9HPT-D and 9HPT-ND) in the first place using the improvement threshold for each of the components defined in Section 3.4.1; then CDI in a multicomponent endpoint (MCE) is determined based on the CDI results of the components that constitute the MCE. Improvement in T25FW, 9HPT-D and 9HPT-ND will be derived after the imputation rules described in Section 5.2.1. are applied.

60-day Relapse Window

A *60-day relapse window* is employed for some conditions in the CDI and CDW derivations. A subject is regarded as having a relapse for at least 60 days after the onset of a protocol-defined relapse. At each (unscheduled) relapse visit, the investigator will evaluate whether the subject experiences a protocol-defined MS relapse. A visit is considered as within the 60-day relapse window if (date of the visit – onset date of the protocol-defined MS relapse) <60 days.

Potential Improvement and Tentative Improvement

For each component, a *potential improvement* is observed at a given visit if the improvement threshold is met at this visit but is not met at the previous visit, and no CDI has been identified up to this visit since study Day 1.

Assessment at any unscheduled visit will not be used for either potential improvement or improvement confirmation.

To be eligible for evaluation of CDI, potential improvement must start in the Part 1 and Part 2 actual treatment period defined in Section 3.3. Visits outside of the Part 1 and Part 2 actual treatment period can only be used to confirm potential improvements that start within the Part 1 and Part 2 actual treatment period. If a potential improvement is observed in the Part 1 and Part 2 actual treatment period but there is no later assessment in the remaining study period, then the improvement cannot be confirmed, and the potential improvement in this case is termed as *tentative improvement*.

Confirmed disability improvement will be assessed as follows.

12-week CDI

The *12-week confirmation visit* in default refers to the visit that should occur, per schedule of events (Appendix III) 12 weeks after the visit with a potential improvement observed. If the default confirmation visit is missing, the next scheduled visit that actually occurs will be used as the 12-week confirmation visit.

For each component, a *12-week CDI* is identified if the improvement threshold for the same component is met again at the 12-week confirmation visit that is ≥74 days after the visit with the potential improvement. The 74 days is the minimum distance between 2 consecutive scheduled visits with a target distance of 84 days and a protocol allowed ±5-day visit window. In the event that the improvement at 12-week confirmation visit is <74 days apart from the potential improvement, or that the result at this visit fails to meet the improvement threshold but is assessed within a 60-day relapse window, the next scheduled visit subsequent to this 12-week confirmation visit can confirm the potential improvement if having an improvement observed.

Though acknowledging that Part 2 visits that collect clinical assessments should occur, per schedule of events (Appendix III), 24 weeks apart from each other nominally instead of 12 weeks, for defining 12-week CDI, a visit that is nominally 24-week after a Part 2 visit that has clinical assessments is the nearest scheduled visit immediately after that Part 2 visit that has clinical assessments, so we would still use the Part 2 visits when defining 12-week CDI and use the term 12-week CDI. If the default confirmation visit is missing, the next scheduled visit that actually occurs will be used as the 12-week confirmation visit.

The Part 1 ET and Part 1 EOS visits are treated as scheduled visits and the corresponding assessments can be used to confirm the potential improvement observed at the latest scheduled visit prior to Part 1 ET or Part 1 EOS regardless of the 74-day requirement. For example, if a subject has a potential improvement followed by a Part 1 ET visit and a Part 1 EOS visit, both with non-missing results, then the result at the Part 1 ET visit will be used to confirm the potential improvement regardless of the number of days between the potential improvement and the Part 1 ET visit. For subjects who enroll into Part 2 they will not have Part 1 EOS visits and their Part 2 Day 1 visits can be treated as Part 1 EOS visits and the corresponding assessments can be used to confirm the potential improvement observed at the last scheduled visit prior to Part 2 Day 1 visit regardless of the 74-day requirement.

The Part 2 ET and Part 2 EOS visits are treated as scheduled visits and the corresponding assessments can be used to confirm the potential improvement observed at the latest scheduled visit prior to Part 2 ET or Part 2 EOS regardless of the 74-day requirement. For example, if a subject has a potential improvement followed by a Part 2 ET visit and a Part 2 EOS visit, both with non-missing results, then the result at the Part 2 ET visit will be used to confirm the potential improvement regardless of the number of days between the potential improvement and the Part 2 ET visit.

CDI in an Individual Component

For a disability assessment (EDSS, T25FW, 9HPT-D or 9HPT-ND) that may be used to constitute an MCE together with other disability assessments, if a subject has a potential improvement that is later confirmed following the criteria aforementioned in this section, then the subject is

considered as *with CDI in this component*, and the potential improvement that gets later confirmed is assigned as the actual *CDI event of the component*.

Time to CDI in an Individual Component

For a given individual component, the time to CDI in this component is defined as the number of days from the study Day 1 to the date of the CDI event of this component as defined above. For subjects without CDI in this component, the time to CDI in this component is censored at the date of the subject's latest scheduled visit in the Part 1 and Part 2 actual treatment period at which the result is non-missing, including the case that the subject is unable to complete this component assessment due to MS-related physical limitations. If a subject has missing value of the individual component at the Day 1/Baseline visit, for example, the subject has no assessment at Day 1, or the result of the assessment at Day 1 is not available due to any other reason, then the censoring date will be set as Day 1. Assessment at any unscheduled visit will not be used to determine the censoring time.

CDI in a Multicomponent Endpoint (MCE)

If a subject is with CDI in one or more components that constitute an MCE, then the subject is considered as *with CDI in this MCE*, and the first CDI event of any component is assigned as the actual *CDI event of the MCE*.

Time to CDI in an MCE

The time to CDI in an MCE is defined as the number of days from the study Day 1 to the date of the first CDI event of the MCE as defined above. For subjects without CDI in this MCE, the time to CDI in this MCE is censored at the latest date among the subject's censoring dates for each component constituting this MCE.

3.4.3.2. Confirmed Disability Worsening (CDW)

CDW is assessed for each of the efficacy components (EDSS, T25FW, 9HPT-D and 9HPT-ND) in the first place using the threshold for each of the components defined in Section 3.4.1; then CDW in an MCE is determined based on the CDW results of the components that constitute this MCE. Worsening in T25FW, 9HPT-D and 9HPT-ND will be derived after the imputation rules described in Section 5.2.1. are applied.

In any case, disability worsening cannot be confirmed if there is a recent relapse and the visit used for confirmation is within a 60-day relapse window as defined in Section 3.4.3.1.

Potential Worsening and Tentative Worsening

For each component, a *potential worsening* is observed at a given visit if worsening threshold is met at this visit but is not met at the previous visit, and no CDW has been identified up to this visit since study Day 1.

An unscheduled visit associated with a protocol-defined MS relapse can be used to identify potential worsening, but cannot be used to confirm a worsening itself. Instead, if following a potential worsening the worsening threshold is met again at this unscheduled relapse visit, then the next visit subsequent to this unscheduled relapse visit will be used for worsening confirmation.

To be eligible for evaluation of CDW, potential worsening must start in the Part 1 and Part 2 actual treatment period defined in Section 3.3. Visits outside the Part 1 and Part 2 actual treatment period can only be used to confirm potential worsening events that start within the Part 1 and Part 2 actual treatment period. If a potential worsening is observed in the Part 1 and Part 2 actual treatment period but there is no later assessment in the remaining study period, then the worsening cannot be confirmed, and the potential improvement in this case is termed as *tentative worsening*.

Confirmed disability worsening will be assessed as follows.

12-week CDW

The *12-week confirmation visit* in default refers to the visit that should occur, per schedule of events (Appendix III), 12 weeks after the visit with a potential worsening observed. If the default confirmation visit is missing, the next scheduled visit or unscheduled relapse visit that actually occurs will be used as the 12-week confirmation visit.

For each component, a *12-week CDW* is identified if the worsening threshold for the same component is met again at the 12-week confirmation visit, which is ≥74 days after the visit with the potential worsening and not within a 60-day relapse window. In the event that the worsening at the 12-week confirmation visit is <74 days apart from the potential worsening or within a 60-day relapse window, the next visit subsequent to this 12-week confirmation visit can confirm the potential worsening if having a worsening observed and not within a 60-day relapse window.

Though acknowledging that Part 2 visits that collect clinical assessments should occur, per schedule of events (Appendix III), 24 weeks apart from each other nominally instead of 12-weeks, for defining 12-week CDW, a visit that is nominally 24-week after a Part 2 visit that has clinical assessments is the nearest scheduled visit immediately after that Part 2 visit that has clinical assessments, so we would still use the Part 2 visits when defining 12-week CDW and use the term 12-week CDW. If the default confirmation visit is missing, the next scheduled visit that actually occurs will be used as the 12-week confirmation visit.

The Part 1 ET and Part 1 EOS visits are treated as scheduled visits and the corresponding assessment can be used to confirm a previous potential worsening if there is no scheduled visit between the potential worsening and the Part 1 ET or Part 1 EOS regardless of the 74-day requirement. For example, if a subject has a potential worsening followed by a Part 1 ET visit and a Part 1 EOS visit, both with non-missing results and not within a 60-day relapse window, then the result at Part 1 ET visit will be used to confirm the potential worsening regardless of the number of days between the potential worsening and the Part 1 ET visit. For subjects who enroll into Part 2 they will not have Part 1 EOS visits and their Part 2 Day 1 visits can be treated as Part 1 EOS visits and the corresponding assessments can be used to confirm a previous potential worsening if there is no scheduled visit between the potential worsening and Part 2 Day 1 visit regardless of the 74-day requirement.

The Part 2 ET and Part 2 EOS visits are treated as scheduled visits and the corresponding assessment can be used to confirm a previous potential worsening if there is no scheduled visit between the potential worsening and the Part 2 ET or Part 2 EOS regardless of the 74-day requirement. For example, if a subject has a potential worsening followed by a Part 2 ET visit

and a Part 2 EOS visit, both with non-missing results and not within a 60-day relapse window, then the result at Part 2 ET visit will be used to confirm the potential worsening regardless of the number of days between the potential worsening and the Part 2 ET visit.

CDW in an Individual Component

For a disability assessment (e.g., EDSS, T25FW) that may be used to constitute an MCE together with other disability assessments, if a subject has a potential worsening that is later confirmed following the criteria aforementioned in this section, then the subject is considered as *with CDW in this component*, and the potential worsening that gets later confirmed is assigned as the actual *CDW event of the component*.

Time to CDW in an Individual Component

For a given individual component, the time to CDW in this component is defined as the number of days from the study Day 1 to the date of the CDW event of this component as defined above. For subjects without CDW in this component, the time to CDW in this component is censored at the date of the subject's latest visit (considering all scheduled visits and unscheduled visit where a protocol-defined MS relapse is asserted) in the Part 1 and Part 2 actual treatment period at which the result is non-missing, including the case that the subject is unable to complete this component assessment due to MS-related physical limitations. If a subject has missing value of the individual component at the Day 1/Baseline visit, for example, the subject has no assessment at Day 1, or the result of the assessment at Day 1 is not available due to any other reason, then the censoring date will be set as Day 1.

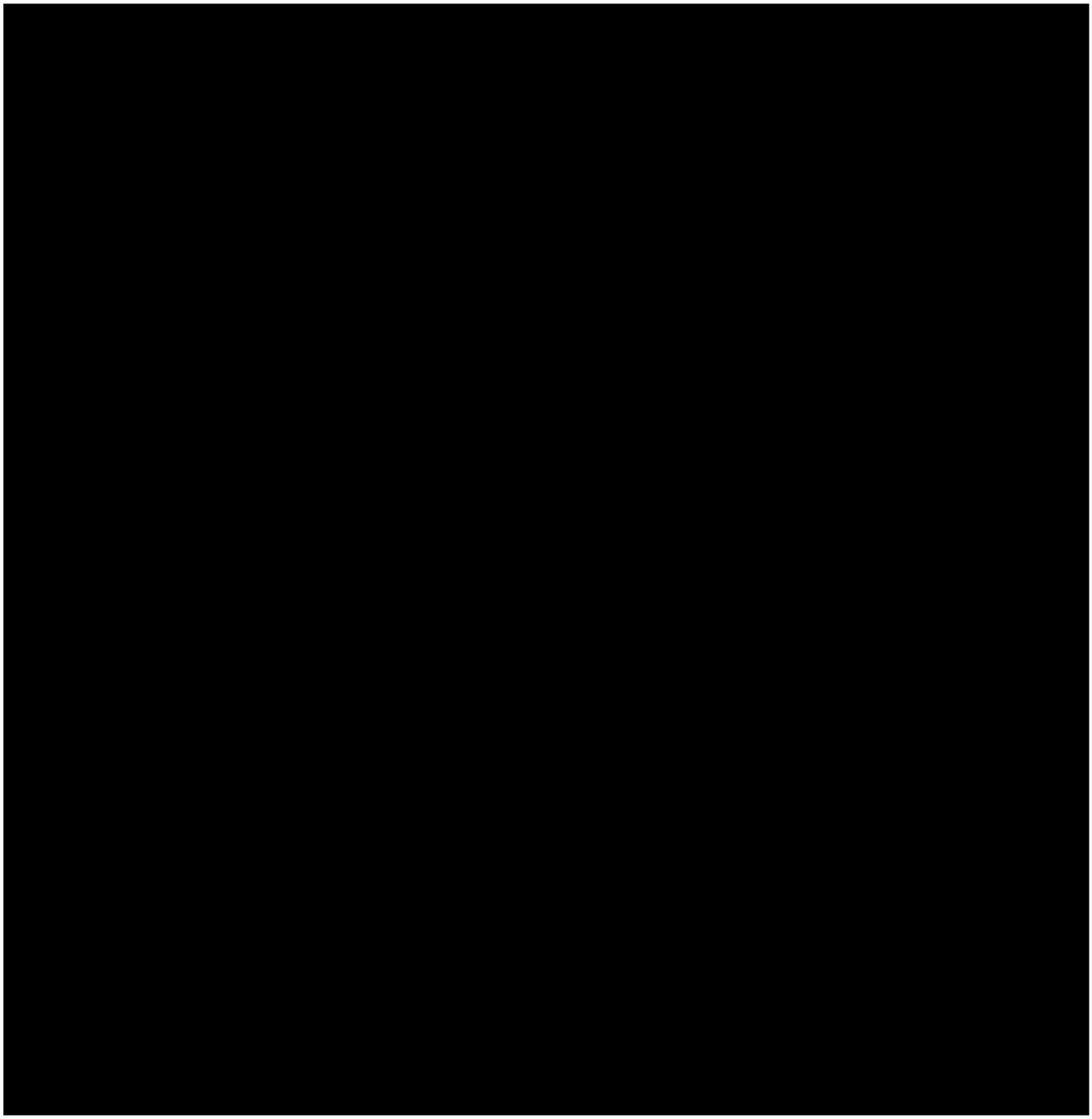
CDW in an MCE

If a subject is with CDW in one or more components that constitute an MCE, then the subject is considered as *with CDW in this MCE*, and the first CDW event of any component is assigned as the actual *CDW event of the MCE*.

Time to CDW in an MCE

The time to CDW in an MCE is defined as the number of days from the study Day 1 to the date of the first CDW event of this MCE as defined above. For subjects without CDW in this MCE, the time to CDW in this MCE is censored at the latest date among the subject's censoring dates for each component constituting the MCE.

[redacted]



3.5. Stratification Factors and Subgroup Variables

3.5.1. Stratification Factors

The randomization stratification factors are listed as follows.

- MS type:
  - Relapsing-remitting MS (RRMS).
  - Secondary progressive MS (SPMS).

- Background DMT group:
  - IFN-β (Avonex, Plegridy®, Betaferon®/ Betaseron®, or Rebif®).
  - dimethyl fumarate (DMF; Tecfidera®).
  - natalizumab (Tysabri®).

  Unless otherwise specified, the background DMT refers to the baseline DMT according to randomization stratification.
- [redacted]

3.5.2. Subgroup Variables

3.5.2.1. Baseline Characteristics Subgroup Variables

- Regions (North America, Eastern Europe, Western Europe and other regions)
  - North America: Canada, United States.
  - Eastern Europe: Czech Republic, Hungary, Poland.
  - Western Europe and other regions: Belgium, United Kingdom, Germany, France, Switzerland, Italy, Netherlands, Spain, Australia, Israel.

[redacted]

- [redacted]
- [redacted]

3.5.2.3. DMT Subgroups

- 1-DMT groups: subjects with background DMT as 1) IFN-β, 2) Dimethyl fumarate, and 3) Natalizumab.
- 2-DMT groups: subjects with background DMT as 1) IFN-β or Dimethyl fumarate, 2) IFN-β or Natalizumab, and 3) Dimethyl fumarate or Natalizumab.

3.6. Analysis Population

Intention-to-treat (ITT) population and safety population are defined as follows:

- **ITT population**
  The ITT population is defined as all subjects who were randomized in Part 1 and received at least 1 dose of study treatment in Part 2. In analyses performed on the ITT population,

subjects will be analyzed according to their randomized treatment assignment in Part 1 regardless of actual treatment received.

- **Safety population**

  The safety population is defined as subjects who were randomized in Part 1 and received at least 1 dose of study treatment in Part 2. Although treatment assignment error in Part 1 is not expected, if some subjects received different study treatment in Part 1 other than the randomization allocation in Part 1, the safety analyses will be based on the actual treatment allocation in Part 1. The actual treatment in Part 1 will be BIIB033 if the subject received any active dose of BIIB033 in Part 1; otherwise, the actual treatment will be placebo.

4. List of Planned Study Analyses

4.1. Interim Analysis

According to the protocol, in Part 2, an interim analysis (IA) may be performed as needed. Subject level data from Part 1 will remain blinded for all subjects and site investigator/staff while Part 2 is ongoing. Before the Part 2 was discontinued in October 2020, no Part 2 IA was actually performed.

[redacted]

5. Statistical Methods for Planned Analyses

5.1. General Principles

Descriptive summary statistics will be presented for all safety endpoints [redacted] For continuous endpoints, descriptive summary statistics will generally include number of subjects with data, the mean, standard deviation, median, interquartile range (Q1, Q3) and range (minimum, maximum). For categorical endpoints, this will generally include number and the percent of subjects with data in each category.

The statistical software, SAS® version 9.4 or above, will be used for all summaries and statistical analyses.

This Statistical Analysis Plan (SAP) document supersedes the statistical section in the protocol and provides details for those analyses pre-specified before database lock. Additional ad hoc analyses may be conducted if needed after database lock and if there are any significant

modification on SAP after database lock, those must be documented in clinical study report (CSR) accordingly.

5.2. Handling of Missing Data

5.2.1. T25FW, 9HPT-D and 9HPT-ND

The following rules will be applied to handle missing data in T25FW and 9HPT before any further analyses or derivations of disability improvement/worsening endpoints.

At each visit, the T25FW assessment has 2 trials and the average time from the 2 trials will be used for statistical analyses.

(1) If a subject misses 1 trial due to reasons other than MS-related physical limitations, the result from the other trial will be used for that visit in the analyses.

(2) If results from both trials are missing due to reasons other than MS-related physical limitations, the T25FW assessment for that visit will be set as missing.

(3) If a subject misses either trial due to MS-related physical limitations, the assessment result (time in seconds) will be imputed as 13.7×SD (reference) + MEAN (reference), where the MEAN (reference) and SD (reference) are the mean and standard deviation of the averaged time from two trials of baseline assessments based on the reference population. The reference population is defined as all subjects dosed with non-missing baseline assessments for at least 1 trial. The baseline assessments used for calculating the average time do not include any trials that are missing due to MS-related physical limitations.

At each visit, the 9HPT assessment will be evaluated on the dominant hand and non-dominant hand separately, and 2 trials will be performed on each hand. For each hand, the average time from the 2 trials will be used for statistical analyses.

(1) If a subject misses 1 trial on one hand due to reasons other than MS-related physical limitations, the result from the other trial will be used for that visit in the analyses.

(2) If results from both trials on one hand are missing due to reasons other than MS-related physical limitations, the 9HPT assessment for that hand will be set as missing at that visit.

(3) If a subject misses either trial on one hand due to MS-related physical limitations, 777 seconds (Fischer, J. et al. (2001)) will be assigned as 9HPT test assessment for the disabled hand at that visit.

When the average of dominant and non-dominant hand is calculated for the combined 9HPT assessment, if the assessment for one hand is missing, the average will be the assessment of the other hand.

5.2.2. Adverse Event and Concomitant Medication

For completely missing start dates of AEs, assign the first dose date of study treatment in Part 1. No imputation will be performed for completely missing start dates of concomitant medications. The partial start dates will be imputed as follows:

- If only the day is missing and month and year are present, then assign to the first day of the month;
- If only the year is present and month and day are missing, then assign to January 1st. The imputed start date will be compared to the first dose date of study treatment in Part 1. If the imputed start date is earlier than the Part 1 first dose date, then the Part 1 first dose date will be chosen.

No imputation will be performed for completely missing end dates of AEs and concomitant medications. The partial end dates will be imputed as follows:

- If only the day is missing and month and year are present, then assign to the last day of the month;
- If only the year is present and month and day are missing, then assign to December 31st. The imputed end date will be compared to the last day in Part 1 and Part 2. If the imputed end date is later than the last day in Part 1 and Part 2, then the last day in Part 1 and Part 2 will be chosen.

5.2.3. MS Relapse

For all relapses, retrieve relapses onset date from relapse assessment data and adverse event termed "Multiple sclerosis relapse" data. All relapses from relapse assessment data will be used. If there is an adverse event termed "Multiple sclerosis relapse" and the start date is different from all relapse onset dates from relapse assessment of the subject, this is considered as a subjective relapse of this subject and the start date of such adverse event is considered as the relapse onset date of a subjective relapse.

The following rules will be used to impute the completely missing or partial onset dates of all relapses:

- If the onset date is from relapse assessment:
    - If the date is completely missing, then assign to the day after the first dose date of study treatment in Part 1;
    - If only the day is missing and month and year are present, then assign to the first day of the month;
    - If only the year is present and month and day are missing, then assign to January 1st;
    - The imputed onset date will be compared to the day after the first dose date in Part 1. If the imputed onset date is earlier than the day after the first dose date in Part 1, then the day after the first dose day in Part 1 will be chosen.
- If the onset date is from adverse event termed "Multiple sclerosis relapse":
    - If the date is completely missing, then assign to the first dose date of study treatment in Part 1;
    - If only the day is missing and month and year are present, then assign to the first day of the month;

- If only the year is present and month and day are missing, then assign to January 1st.
- The imputed start date will be compared to the first dose date of study treatment in Part 1. If the imputed start date is earlier than the first dose date in Part 1, then the first dose date in Part 1 will be chosen.

Protocol-defined relapse is also used for efficacy analysis. Since the protocol-defined relapse date is from relapse assessment data, the imputation will follow the rule above for imputing the onset date if the onset date is from relapse assessment.

5.3. Accounting of Subjects

The summary of subject disposition will include: subjects randomized in Part 1, subjects entering into Part 2; subjects dosed in Part 2; subjects who completed the treatment for 24 weeks in Part 2; subjects who completed the treatment for 48 weeks in Part 2; subjects who completed the treatment for 72 weeks in Part 2; subjects who completed the treatment for 96 weeks in Part 2; subjects who completed the Part 2; subjects who discontinued study treatment in Part 2 and the reasons for discontinuation; and subjects who withdrew from study in Part 2 and the reasons for withdrawal. A listing of those subjects who discontinued study treatment/withdraw from study in Part 2 and the associated reasons for discontinuation/withdrawal will be presented by the treatment group to which they are randomized in Part 1 (i.e., randomized treatment group). A listing of randomized subjects excluded from ITT population will be presented. Number of subjects in each analysis population (i.e., ITT population and safety population) will also be summarized. In addition, number of subjects dosed in Part 2, number of subjects who completed the study in Part 2 in each randomized treatment group and overall will be summarized by country and sites. Number of subjects in Part 2 by background DMT group and by region will be presented by randomized treatment groups and overall.

The summary of subjects on stratification factors (MS type, background DMT group and imaging core group/imaging non-core group) will be summarized separately by the randomized treatment groups and overall.

The number of subjects whose Part 2 visits are impacted by the pandemic, including missing or out-of-window study treatment and key efficacy assessments will be summarized, according to information recorded in the study protocol deviation listing. Due to COVID-19 pandemic measures, there may be challenges to conduct on-site monitoring visits and therefore result in some study data pending source data verification (SDV). The number of subjects who have any pending SDV data and the number of study visits without SDV performed will be presented.

5.4. Demographic and Baseline Characteristics

All demographics and baseline disease characteristics will be summarized for ITT population. Unless otherwise specified, baseline refers to the baseline in Part 1. Also, demographic and baseline disease characteristics data are not collected at baseline in Part 2 on the CRF.

Demographic data, including age (in years), age category (<18, 18-30, 31-40, 41-50, 51-58, >58) and (<40, ≥40), and gender will be summarized by randomized treatment groups and overall, also by randomized treatment groups and background DMT group.

Baseline MS disease history will be summarized by randomized treatment groups and overall, using descriptive statistics. Time since onset of MS symptoms (in years), time since MS diagnosis (in years), number of subjects with secondary progressive MS (SPMS), time since onset of secondary progressive MS (in months, for subjects with SPMS only), time since the most recent relapse prior to Part 1 Day 1 (in months), [redacted]

Number and percentage of subjects with any MS treatment history will be summarized by randomized treatment groups and overall. Specifically, number and percentage of subjects who have taken approved DMTs and others will also be displayed by randomized treatment groups and overall. Approved DMTs to be listed include alemtuzumab, cladribine, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferons (Interferon Beta-1A(AVONEX), Interferon Beta-1A (REBIF), Interferon Beta-1B (EXTAVIA)), Interferon Beta-1B (BETASERON), Peginterferon Beta-1A (PLEGRIDY), natalizumab, ocrelizumab, and teriflunomide.

[redacted]

Medical history will be coded using the latest version of MedDRA (version 23.0 or later if updated) and number and percentage of subjects with each history will be presented using the preferred term.

5.5. Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a protocol deviation log and categorized as major or minor deviations. Number and percentage of subjects with at least one major deviation in Part 2 will be summarized by category. All protocol deviations in Part 2 related to COVID-19 pandemic measures will be provided in a listing with all available details.

5.6. Study Treatment Exposure and Concomitant Medications

Extent of exposure to study treatment will be summarized for the ITT population. Number of infusions taken throughout Part 1 and Part 2 will be summarized as both continuous and category variables (>=12, >=16, >=18, >=22, >=26, >=30, >=34, >=38, >=42, >=44). Number of infusions taken in Part 2 will be summarized as both continuous and category variables (1, 2, 3, …, 25). The overall study drug compliance in Part 2 and study drug compliance during treatment phase in Part 2 will be provided. Subjects will also be categorized and summarized by "without missing any dose in Part 2", "missed 1 dose in Part 2" and "missed >1 dose in Part 2".

Overall study drug compliance in Part 2

Defined as the percentage of study drug infusions actually received over 25 planned doses for 96 weeks, will be summarized regardless of study completion for all subjects.

Study drug compliance during treatment phase in Part 2

Defined as number of infusions actually received divided by the number of expected; the expected infusions is the total 25 planned doses for those who completed 96 weeks of study treatment in Part 2, and is the total number of planned doses before early termination visit date for those who early terminated in Part 2.

The total number of weeks on study drug in Part 1 and Part 2 for each subject will be summarized as a continuous variable and presented in groups of 12-week intervals. Weeks on study drug in Part 1 and Part 2 are calculated as the number of weeks from the first dose date in Part 1 to the last dose date in Part 2 plus 4 weeks. Days on study drug in Part 1 and Part 2 are calculated as the number of days from the first dose date in Part 1 to the last dose date in Part 2 plus 28 days. The total number of weeks on study drug in Part 2 for each subject will also be summarized as a continuous variable and presented in groups of 4-week intervals. Weeks on study drug in Part 2 are calculated as the number of weeks from the first dose date in Part 2 to the last dose date in Part 2 plus 4 weeks. Days on study drug in Part 2 are calculated as the number of days from the first dose date in Part 2 to the last dose date in Part 2 plus 28 days.

Concomitant therapy will be summarized for the ITT population.

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary (WHODD GLOBAL version B3 March 2020, or later if updated). Concomitant medication is any drug or substance administered between first dose date in Part 2 and the Part 2 EOS date. A concomitant non-drug treatment is any therapeutic interventions or diagnostic assessment performed between the first dose date in Part 2 and the Part 2 EOS date.

A medication in Part 1 refers to a medication that starts prior to the Part 2 Day 1 dose date. A medication in Part 2 refers to a medication that starts on or after the Part 2 Day 1 dose date. If a subject is not enrolled in Part 2 or is enrolled in Part 2 but never receives infusion of study treatment in Part 2, all medications will be considered as occurring in Part 1.

A medication and/or non-drug treatments in Part 2 is regarded as concomitant with study treatment in Part 2 of the study if the stop date/time is on or after the first dose date/time of study treatment in Part 2. In order to determine whether medication and/or non-drug treatments with missing stop dates are concomitant, the following additional criteria will be used:

- If stop date of a particular therapy has year, month available but day missing and the year and month of the stop date is on/after the first dose date in Part 2, then the therapy will be considered as concomitant in Part 2;
- If stop date of a particular therapy has year available but month and day missing and the year is on/after the first dose date in Part 2, then the therapy will be considered as concomitant in Part 2.

If stop date of a particular therapy is missing, then the therapy will be considered as concomitant in Part 2. The number and percent of subjects taking concomitant medication and non-drug treatments will be summarized separately by randomized treatment groups and overall.

5.7. Efficacy Endpoints

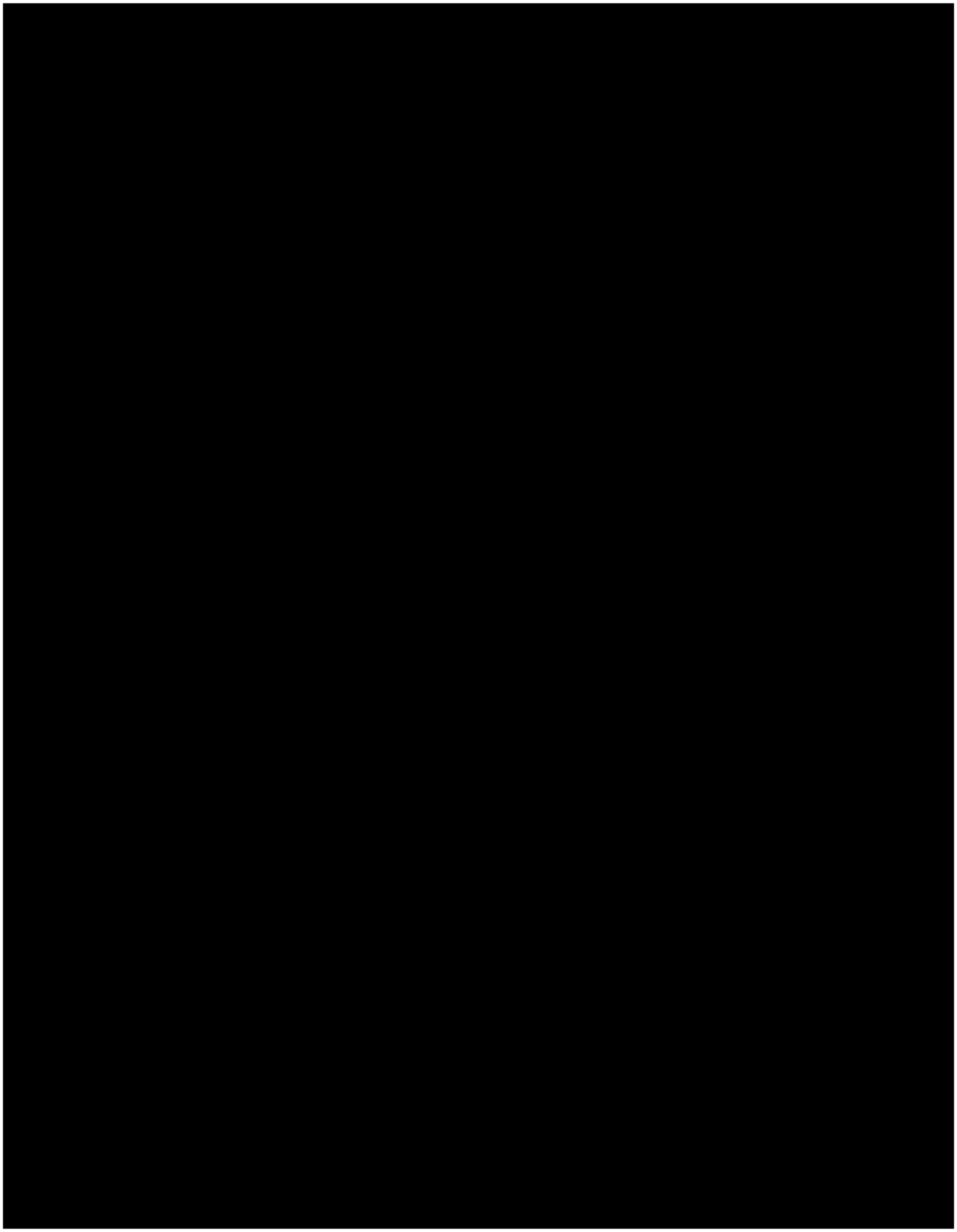
5.7.1. General Analysis Methods for Efficacy Endpoints

Part 1 failed to meet its primary endpoint, ORS over 72 weeks and secondary endpoints, 12-week CDI. Subsequently, the sponsor made the decision to early terminate Part 2 study.

[redacted]

Study protocol specifies that disallowed concomitant therapies include: 1) more than one background DMT at any time, including any chronic immunosuppressant or immunomodulatory therapy; 2) any investigational product; 3) any systemic steroid therapy without prior approval from the Sponsor, except for protocol-defined treatment of relapses. The blinded clinical review of all concomitant therapies data collected during Part 1 and Part 2 shows that one subject received immunosuppressant treatment (methotrexate) as a concomitant medication during the Part 1. One subject received immunosuppressant treatment (cisplatin/pemetrexed) as a concomitant medication during the Part 2. No subject received investigational therapy. One subject who received high dose (1000 mg) systemic steroid treatments monthly as a concomitant medication in Part 1. There were other subjects who received systemic steroid treatments for various medical reasons but not for protocol-defined relapses, all cases were a single course for one week or less, which were considered to have minimal impact on the efficacy analyses. Therefore, in the efficacy analyses, only immunosuppressant treatment (methotrexate), immunosuppressant treatment (cisplatin/pemetrexed) and monthly high dose (1000 mg) systemic steroid treatments are considered as prohibited concomitant therapy in Part 1 and/or Part 2. Data on efficacy endpoints of a study subject collected after the use of methotrexate, of a study subject collected after the use of cisplatin/pemetrexed, and of a study subject collected after the monthly high dose (1000 mg) systemic steroid treatments will not be included in any efficacy analyses for each of these three subjects.

In general, the protocol specified efficacy endpoints assessed in Part 2 will not be analyzed. [redacted] There will be no statistical inference for any efficacy endpoints.



[redacted]

5.8. Safety Endpoints

5.8.1. General Analysis Methods for Safety Endpoints

All safety endpoints will be evaluated in the safety population (all subjects dosed) as defined in Section 3.6.

All treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), clinical laboratory abnormalities, vital sign measurements, physical examination findings, 12-lead ECG readings, MS signs and symptoms, annualized relapse rate, body weight, Columbia Suicide Severity Rating Scale (C-SSRS), lipid profile, T3, FT4, TSH will be evaluated for safety based on Part 2 safety data. For clinical laboratory abnormalities, vital sign measurements, physical examination findings, 12-lead ECG readings, MS signs and symptoms, annualized relapse rate, body weight, C-SSRS, lipid profile, T3, FT4 and TSH, the safety data collected at Part 2 scheduled visits and unscheduled visits where the date is on or after Part 2 Day 1 infusion day will be used in the analysis.

For safety data that are summarized by visit, assessments from all scheduled visits, Part 1 ET visit, Part 1 EOS visit and unscheduled visits in Part 1 and all scheduled visits, Part 2 ET visit, Part 2 EOS visit and unscheduled visits in Part 2 will be mapped to an appropriate analysis visit using a windowing scheme (Section 3.2).

5.8.2. Adverse Events

For this study, any TEAE experienced by the Part 2 enrolled subject between the time of first dose of study treatment in Part 2 and the EOS visit in Part 2 is to be recorded on the CRF,

regardless of the severity of the event or its relationship to study treatment. Any SAE experienced by the Part 2 enrolled subject between the time the subject has signed the ICF and the EOS visit in Part 2 is to be recorded, regardless of the severity of the event or its relationship to study treatment.

All AEs will be coded using MedDRA (version 23.0 or later if updated) and will be analyzed based on the principle of treatment emergence.

In order to define treatment-emergent AEs with completely missing/partial start or end dates, the following additional criteria will be used:

- If both the start and end dates for a particular event are completely missing, then that event is considered treatment emergent in Part 2;
- If the start date for a particular event is completely missing, then the end date/time will be compared to the Part 2 first dose date:
    - If the end date/time is complete and is on or after the Part 2 first dose date/time, then that event is considered as treatment emergent in Part 2;
    - If the end time is missing, but the end date is present and is on or after the Part 2 first dose date, then that event is considered as treatment emergent in Part 2;
    - If the end day is missing, but the year/month of end date is present and is on or after that of the Part 2 first dose date, then that event is considered as treatment emergent in Part 2;
    - If only the year of end date is present and is on or after that of the Part 2 first dose date, then that event is considered as treatment emergent in Part 2;
- If the start date for a particular event is partially missing, and the year/month/day of the event date will be compared to that of the Part 2 first dose date:
    - If the start time is missing and year/month/day of the start date falls after that of the Part 2 first dose date, then that event is considered treatment emergent in Part 2;
    - If the start day is missing and year/month of the start date falls after that of the Part 2 first dose date, then that event is considered treatment emergent in Part 2;
    - If only the year of the start date is present and falls after that of the Part 2 first dose date, then that event is considered as treatment emergent in Part 2.
    - If the partial start date is the same as that of the Part 2 first dose date, then the end date/time will be compared to the Part 2 first dose date following the logic above.

The overall summary table of TEAEs will present the number of subjects with the following events by randomized treatment groups. A subject is counted only once in each category. All treatment-emergent adverse event and treatment-emergent serious adverse events will be presented and summarized.

- Any TEAE;

- TEAE with severity as "moderate" or "severe";
- TEAE with severity as "severe";
- Current DMT related TEAE;
- Study treatment related TEAE;
- Any SAE;
- Current DMT related SAE;
- Study treatment related SAE;
- AE leading to discontinuation of study treatment;
- AE leading to withdrawal from study.

The incidence of TEAEs will be summarized using the primary system organ class (SOC) and preferred term (PT). Preferred terms are presented by decreasing incidence in the BIIB033 column within each system organ class.

The incidence of TEAEs will also be summarized by event severity and by relationship to study drug using system organ class and preferred term. Within each system organ class or/and preferred term, the same subject will be counted only once. Under the same system organ class or/and preferred term, the occurrence of the adverse event with the greatest severity will be used in the calculation of incidence by severity; the occurrence of the adverse event with the strongest relationship to study drug will be used in summarizing incidence by relationship to study drug.

Additionally, the incidence of TEAEs will be summarized by using preferred term only, and preferred terms will be ordered by decreasing frequency of AEs in the BIIB033 column.

The incidence of treatment-emergent SAEs will also be summarized by primary system organ class, preferred term and randomized treatment group as well.

Listings of TEAEs, treatment-emergent SAEs, TEAEs that led to study drug discontinuation, and TEAEs that led to study withdrawal will be presented. Listing of death will be provided if applicable.

In some TEAE/treatment-emergent SAE listings, complete TEAE start and end dates are needed to calculate the relative study days of AE start and end. Therefore, any partial date will be imputed for these listings as described in Section 5.2.2.

TEAEs around the time of infusion

The incidence of TEAEs around the time of the infusion (within 4 hours and 24 hours post start of infusion respectively) will be summarized by preferred term and visit for each randomized treatment group. At each visit, the same subject will be counted only once within each preferred term. Preferred terms will be ordered by decreasing frequency of TEAEs in the BIIB033 column.

Listings of such TEAEs around the time of the infusion (within 4 hours and 24 hours after infusion start respectively) will be provided by randomized treatment group.

AEs starting on or after Part 2 Day 1 infusion day that are not TEAEs

Listing of AEs that starts on or after Part 2 Day 1 infusion day that are not TEAEs will be presented in a separate listing, if applicable. Any partial start date will be imputed as described in Section 5.2.2., before comparing to Part 2 Day 1 infusion day.

AEs starting before Part 2 Day 1 infusion day that are not reported in Part 1 analysis

All AEs experienced by the subject between the time of first dose of study treatment in Part 1 and Part 2 Day 1 - 1 for those who enroll in Part 2 are expected to have been recorded on the CRF of Part 1 database lock and reported in Part 1 analysis. However, there can be AEs that are recorded on the CRF after Part 1 database lock, but the starting time is before Part 2 Day 1 infusion day (i.e., the starting time is on or prior to Part 2 Day 1 -1). The AEs recorded on the CRF will be compared to the AEs recorded on the CRF of Part 1 database lock in terms of starting time and preferred term, and any AEs starting before Part 2 Day 1 infusion day that are not reported in Part 1 analysis will be presented in a listing.

5.8.3. MS Relapse

If an MS relapse is suspected during the study, an unscheduled visit should be performed to confirm the relapse and assess the severity, which will be documented in the relapse assessment form.

Summary will be made for all relapse (including protocol-defined, non-protocol-defined, and subjective relapse) as well as protocol-defined relapse only. A summary table will be displayed with the number of subjects with 0, 1, 2, 3 or >3 relapse by randomized treatment groups. The total number of relapse and subject-years followed will be shown in the table. Total number of subject-year is defined as the sum of number of days of all subjects in the study divided by 365.25. Unadjusted annualized relapse rate is the total number of relapses of all subjects in the study divided by the total subject-year.

5.8.4. Clinical Laboratory Abnormalities

The following clinical laboratory parameters are assessed at all study visits as stated in Section 5 and Section 14.2 of the protocol:

- Hematology: complete blood count with differential and platelet count, and absolute neutrophil count. Prothrombin time (PT), partial thromboplastin time (PTT) and platelets will also be measured for all subjects on Part 2 Day 1 and at each visit when hematology is done.
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), gamma-glutamyl-transferase (GGT), glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium and follicle-stimulating hormone (FSH: for postmenopausal female subjects only).
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal).
- Serum and urine pregnancy test (women of child-bearing potential only).

Baseline value in Part 2 is defined as in Section 3.3.

Shift analyses

Laboratory data (except coagulation) will be summarized using shift tables where appropriate. Each subject's hematology and blood chemistry values will be flagged as "low", "normal", or "high" based on the normal ranges of the central laboratory or as "unknown" if no result is available. Each subject's urinalysis values will be flagged as "positive" (or "low"/"high"), "negative" (or "normal"), or "unknown". Shifts from Part 2 baseline to high or low status for hematology and blood chemistry parameters, and shifts from Part 2 baseline to high or positive status for urinalysis will be presented.

In the hematology and blood chemistry shift summary tables, entries are numbers of subjects shift to low (or high) divide by number of subjects at risk followed by corresponding percentages. Number at risk for shifting to low (or high) is the number of subjects whose Part 2 baseline value was not low (or high) and who had at least one post-baseline evaluation. Shift to low includes normal to low, high to low, and unknown to low. Shift to high includes normal to high, low to high, and unknown to high.

In the urinalysis shift summary table, entries are numbers of subjects shift to high or positive divided by number of subjects at risk followed by corresponding percentages. Number at risk for shift to high or positive is the number of subjects whose Part 2 baseline value was not high or positive and who had at least one post-baseline evaluation. Shift to high or positive includes low to high, normal or negative to high or positive and unknown to high or positive.

The following rule will be used to determine the abnormality for urine test result of "Trace".

- For Urine Blood test, if subject is female and test result is "Trace", then it is considered as Normal/Negative;
- For other urine tests, if test result is "Trace", then it is considered as High/Positive.

A listing will be presented for all subjects with post-baseline urinalysis shifts. In this listing, each subject's complete values for that specific urine test from Part 2 Day 1 to last study visit will be listed with shifts labeled.

Liver function laboratory tests

For liver function laboratory tests (ALT, AST, and total bilirubin), count and percentage of maximal post-baseline values by following categories will be provided:

For ALT or AST,

- $\leq$ Upper Limit of Normal (ULN),
- >ULN,
- $\geq$ 3x ULN,
- >5x ULN,
- >10x ULN,
- >20x ULN.

For total bilirubin,

- ≤ ULN,
- >ULN,
- ≥ 1.5x ULN,
- >2x ULN.

For more than one liver function test

- ALT or AST ≥ 3x ULN and total bilirubin ≥ 1.5x ULN at the same time point,
- ALT or AST ≥ 3x ULN and total bilirubin >2x ULN at the same time point.

A subject listing will be presented for all subjects with any post-baseline ALT or AST ≥ 3x ULN. In this listing, each subject's detailed liver function test values (total bilirubin, alkaline phosphatase, ALT/SGPT, AST/SGOT, GGT) from Part 2 Day 1 to last study visit will be listed with abnormal records labeled.

Summary and listings of actual values and change from baseline

Actual laboratory values, changes from baseline and percent changes from baseline in selected quantitative laboratory values will be summarized using descriptive statistics by randomized treatment group and visit. Box and whisker plots displaying values and changes from baseline by visit will also be presented.

Potentially clinically significant (PCS) abnormalities

For hematology and blood chemistry, the number and percentage of subjects with any post-baseline PCS laboratory abnormalities will be summarized by randomized treatment group for the parameters provided in **Table *2***.

Subject listings will also be presented for all subjects with any PCS laboratory abnormalities. In these listings, each subject's complete history from Part 2 Day 1 to last study visit for that specific laboratory test meeting the PCS criteria will be listed; any abnormal values based on the normal ranges of the central laboratory and abnormal values based PCS criteria will be separately flagged in the same listing.

Table 2: Laboratory PCS Criteria (Adult)

Parameter Name	Unit	PCS Low	PCS High
Hematology			
White Blood Cells	$x10^9$ cells/L	<3.0	>16
Neutrophils	$x10^9$ cells/L	<1.5	>13.5
Lymphocytes	$x10^9$ cells/L	<0.8	>12
Monocytes	$x10^9$ cells/L	N/A	>2.5

Eosinophils	$x10^9$ cells/L	N/A	>1.6
Basophils	$x10^9$ cells/L	N/A	>1.6
Hemoglobin for females for males	g/L	≤ 95 ≤ 115	≥175 ≥190
Hematocrit for females for males	%	≤ 32 ≤ 37	≥54 ≥60
Red Blood Cells (RBC)	$x10^{12}$ cells/L	≤ 3.5	≥6.4
Platelet count	$x10^9$ cells/L	≤ 75	≥700
Chemistry			
Sodium	mmol/L	≤ 126	≥ 156
Potassium	mmol/L	≤ 3	≥ 6
Chloride	mmol/L	≤ 90	≥ 118
Bicarbonate	mmol/L	≤ 16	≥ 35
Calcium	mmol/L	≤ 2	≥ 3
Phosphorous	mmol/L	≤ 0.5491	≥ 1.7119
Aspartate aminotransferase (AST)	IU/L	N/A	≥ 3x ULN
Alanine Aminotransferase (ALT)	IU/L	N/A	≥ 3x ULN
Alkaline phosphatase	IU/L	N/A	≥ 3x ULN
Creatinine	umol/L	N/A	≥ 1.5x ULN
Total Bilirubin	umol/L	N/A	≥ 1.5x ULN
Total Protein	g/L	≤ 45	≥ 100
Albumin	g/L	≤ 25	N/A
Uric Acid for females	umol/L	N/A	≥ 501.5

for males		N/A	≥ 619.5
Glucose (non-fasting)	mmol/L	≤ 2.2	≥ 13.75

5.8.5. Vital Sign Measurements

Vital signs are collected at all study visits except that height is obtained at Part 2 Day 1 visit only. The analysis of vital signs will focus on the incidence of clinically relevant abnormalities from Part 2 Day 1 to the Part 2 EOS visit. The criteria for clinically relevant post-baseline abnormalities are given in **Table 3**.

Table 3: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C or an increase from baseline of at least 1°C
Pulse	>100 beats per minute (bpm) or an increase from baseline of >30 bpm <40 bpm or a decrease from baseline of >20 bpm
Systolic Blood Pressure	>160 mmHg or an increase from baseline of >40 mmHg <90 mmHg or a decrease from baseline of >30 mmHg
Diastolic Blood Pressure	>100 mmHg or an increase from baseline of >30 mmHg <45 mmHg or a decrease from baseline of >20 mmHg

A summary table for subjects with any clinically relevant post-baseline abnormalities will be provided. In the summary table, entries are numbers of subjects with an abnormality divided by number of subjects evaluated followed by corresponding percentages. Number evaluated is the number of subjects who had a Part 2 baseline assessment and at least one post-baseline assessment for that vital sign.

The number and percentage of subjects with post-baseline weight change of greater than 7% from baseline will be summarized by randomized treatment group and visit. A subject listing of post-baseline weight change of greater than 7% from baseline will be presented.

For temperature, pulse, systolic blood pressure, diastolic blood pressure, respiratory rate and weight, actual values and changes from baseline will be summarized using descriptive statistics by randomized treatment group and visit. Box and whisker plots displaying values and changes from baseline by visit will also be presented.

A subject listing will be presented for subjects with any post-baseline clinically relevant abnormalities in vital signs. In this listing, each subject's complete vital sign values from Part 2 Day 1 to last study visit will be listed with abnormalities labeled.

5.8.6. Physical Examination

Physical examination is performed every 24 weeks from Part 2 Day 1 to Part 2 Week 96, and at Part 2 ET visit, at Part 2 EOS visit and at unscheduled visits. The result collected on CRF at

scheduled visits will be listed as performed or not performed, and abnormality will be reported as AE.

5.8.7. 12-lead ECG Readings

ECG is assessed at Part 2 Screening, and every 12 weeks from Part 2 Day 1 to Part 2 108, and at Part 2 ET visit and at Part 2 EOS visit. The ECG result is classified as "normal", "abnormal", "abnormal, not adverse event", or "abnormal, adverse event".

Status change in ECG from Part 2 Day 1 at Part 2 Week 12, Part 2 Week 24, Part 2 Week 36, Part 2 Week 48, Part 2 Week 60, Part 2 Week 72, Part 2 Week 84, Part 2 Week 96 and Part 2 Week 108 will be summarized using shift tables. The number and percent of subjects with shifts from normal to abnormal values ("abnormal, not adverse event", or "abnormal, adverse event") will be summarized by randomized treatment group.

A listing of details for abnormal ECG findings will also be presented.

5.8.8. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is an assessment that evaluates suicidal ideation and behavior. C-SSRS measurements are collected with respect to "Since last visit" at Part 2 Screening, Part 2 Day 1, Part 2 Week 24, Part 2 Week 48, Part 2 Week 72, Part 2 Week 96, Part 2 Week 108, Part 2 ET visit and Part 2 EOS visit.

There are 12 common "Yes/No" questions at Part 2 baseline and post-baseline visits. Five questions on *suicidal ideation* and six questions on *suicidal behavior* are re-ordered and follow increasing severity order respectively as shown in **Table 4**; another question on *self-injurious behavior without suicidal intent* is listed separately. In particular, only subjects who answered "Yes" to question 2 will proceed to question 3, 4 and 5. Thus, for any subjects who answered "No" to question 2, an answer "No" will also be assumed to question 3, 4, and 5.

Table 4: C-SSRS re-ordered questions

Suicidal Ideation	
Question 1	Wish to be dead
Question 2	Non-specific active suicidal thoughts
Question 3	Active suicidal ideation with any methods (not plan) without intent to act
Question 4	Active suicidal ideation with some intent to act, without specific plan
Question 5	Active suicidal ideation with specific plan and intent
Suicidal Behavior	
Question 6	Preparatory acts or behavior

Question 7	Aborted attempt
Question 8	Interrupted attempt
Question 9	Actual attempt
Question 10	Suicidal behavior
Question 11 (available at Part 2 baseline and post-baseline visits)	Suicide
Self-Injurious Behavior without Suicidal Intent	
Question 12	Self-injurious behavior without suicidal intent

A subject is considered to have *suicidal ideation* at the period of interest if a "Yes" is answered to any of the five suicidal ideation questions (Question 1-5). A subject is considered to have *suicidal behavior* at the period of interest if a "Yes" is answered to any of the six suicidal behavior questions (Question 6-11) at Part 2 baseline or a "Yes" is answered to any of the six suicidal behavior questions (Question 6-11) at post-baseline visit.

A subject's *Suicidal Ideation Score* is defined as the maximal suicidal ideation question number (maximal of 1-5) with an answer "Yes" per visit. The score is defined as 0 if the subject answered "No" to all 5 Suicidal Ideation questions at that visit. A subject is considered to have treatment-emergent suicidal ideation if the subject had either new or worsening suicidal ideation. A subject is considered to have new suicidal ideation if the subject's Suicidal Ideation Score increased at any post-baseline visit compared to a score 0 at Part 2 baseline. A subject is considered to have worsening suicidal ideation if the subject's Suicidal Ideation Score increased at any post-baseline visit compared to a positive score at Part 2 baseline.

A subject is considered to have treatment-emergent suicidal behavior if the subject answered "Yes" to any suicidal behavior questions at any post-baseline visit while answered "No" to all suicidal behavior questions at Part 2 baseline.

The following analyses on C-SSRS measurements will be conducted:

- Descriptive summary of subjects who answered "Yes" to any question 1-12 as well as subjects who had suicidal ideation or suicidal behavior at Part 2 baseline and at any post-baseline visit. The denominator for baseline summary is the number of subjects who were dosed and had baseline assessment; the denominator for post-baseline summary is the number of subjects who were dosed and had at least one post-baseline assessment for each question.
- Descriptive summary of subjects who had treatment-emergent suicidal ideation, subjects who had new suicidal ideation as well as subjects who had worsening suicidal ideation. The denominator is the number of dosed subjects with both baseline and at least one post-baseline suicidal ideation assessment.

- Descriptive summary of subjects who had treatment-emergent suicidal behavior. The denominator is the number of subjects who answered "No" to all suicidal behavior questions at Part 2 baseline and had at least one post-baseline suicidal behavior assessment.

Listing of subjects having treatment-emergent suicidal ideation will be provided. Subjects who had new suicidal ideation and subjects who had worsening suicidal ideation will be flagged. The listing will display both Part 2 baseline and post-baseline Suicidal Ideation Scores for each subject. Listing of subjects having treatment-emergent suicidal behavior will also be provided.

5.8.9. MS Signs and Symptoms

Typical MS signs and symptoms are evaluated at Part 2 Screening, Part 2 baseline and every24 week up to Part 2 Week 96, and at unscheduled visit, Part 2 ET visit, Part 2 EOS visit. MS signs and symptoms are listed in 7 classes as well as sensory disturbances and motor disturbances. Number and percentage of subjects having each listed MS signs and symptoms at each visit will be displayed by randomized treatment groups.

[redacted]

6. Changes from Protocol-Specified Analyses

6.1. Change in the Planned Analysis

Study Part 1 failed to meet its primary endpoint ORS over 72 weeks. The trial also failed to show efficacy in its secondary endpoints. As a result, the sponsor decided to early terminate Part 2 of the study.

[redacted]

[redacted]

6.1.1. Secondary Efficacy Endpoints

Analysis of Secondary Efficacy Endpoint

The protocol specified secondary efficacy endpoints Overall Response Score (ORS) over 96 weeks in Part 2 and proportion of 24-week CDI in Part 2 will not be analyzed.

[redacted]

6.2. COVID-19 Related Analyses

In 2020 there is a worldwide outbreak of respiratory disease named as "Coronavirus Disease 2019" (COVID-19). It has been recognized that this COVID-19 public health emergency may impact the conduct of clinical trials of medical products and the challenges caused by the COVID-19 pandemic may lead to difficulties in meeting protocol-specified procedures,

including administering the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing (FDA 2020 and EMA 2020).

For this study 215MS202, majority of the study Part 1 conduct and data collection have completed by the time of the COVID-19 outbreak. No subject visit from Day 1 to Week 72 is impacted by the COVID-19 pandemic but there are small number of subjects whose Week 84/EOS or Part 2 Day 1 visits are impacted. In Part 1, there were also challenges to conduct on-site monitoring visits and thereof result in some study data pending source data verification (SDV).

Study Part 2 was ongoing at the time of the COVID-19 outbreak, therefore study Part 2 conduct and data collection have been impacted by the time of the COVID-19 outbreak. In Part 2, there were also challenges to conduct on-site monitoring visits and thereof result in some study data pending source data verification (SDV).

For study Part 1, the analyses to assess the impact of COVID-19 pandemic have been described in 215MS202 SAP V2.0.

For assessing the impact of COVID-19 pandemic on Part 2 study conduct and data collection, the following analyses are added. Summaries of study subjects with visits impacted, protocol deviation, missing or out-of-window key disability assessments, missing or out-of-window study drug infusion due to COVID-19 pandemic are to be provided. The incomplete SDV on dosing information and key disability assessments due to the pandemic will also be summarized by visit.

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

Not applicable as there is no previous version of the SAP.

8. References

[1] Dmitrienko, A., Chuang-Stein, C., & D'Agostino, R. B. (2007). **Pharmaceutical statistics using SAS: a practical guide.** SAS Institute.

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[3] FDA Guidance for Industry: Statistical considerations for clinical trials during the COVID-19 public health emergency (2020)

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[6] Lublin, F. D., & Reingold, S. C. (1996). **Defining the clinical course of multiple sclerosis results of an international survey.** Neurology, 46(4), 907-911.

[7] Polman, C. H et al. (2005). **Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria".** Annals of neurology, 58(6), 840-846.

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APPENDICES

Appendix I Visit Window Mapping

Table 5: Visit Windows

EDSS, T25FW, 9HPT, [redacted] Physical Exam		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Part 1		
Baseline	Day 1	Day 1 being the first day of dosing
Week 12	Day 85	Day 2 to Day 127
Week 24	Day 169	Day 128 to Day 211
Week 36	Day 253	Day 212 to Day 295
Week 48	Day 337	Day 296 to Day 379
Week 60	Day 421	Day 380 to Day 463
Week 72	Day 505	Day 464 to Day 547
Week 84	Day 589	≥Day 548
Part 2		
Part 2 Day 1	Part 2 Day 1	Day -5 to Day 5 of Part 2
Part 2 Week 24	Part 2 Day 169	Day 6 to Day 253 of Part 2
Part 2 Week 48	Part 2 Day 337	Day 254 to Day 421 of Part 2
Part 2 Week 72	Part 2 Day 505	Day 422 to Day 589 of Part 2
Part 2 Week 96	Part 2 Day 673	Day 590 to Day 715 of Part 2
Part 2 Week 108	Part 2 Day 757	≥Day 716 of Part 2
NOTE: These assessments are measured every 12 weeks in Part 1. These assessments are measured every 24 weeks up to Part 2 Week 96 and then at Part 2 Week 108 in Part 2.		

Weight		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Part 1		
Baseline	Day 1	Day 1 being the first day of dosing
Week 12	Day 85	Day 2 to Day 127
Week 24	Day 169	Day 128 to Day 211
Week 36	Day 253	Day 212 to Day 295
Week 48	Day 337	Day 296 to Day 379
Week 60	Day 421	Day 380 to Day 463
Week 72	Day 505	Day 464 to Day 547
Week 84	Day 589	≥Day 548
Part 2		

Part 2 Day 1	Part 2 Day 1	Day -5 to Day 5 of Part 2
Part 2 Week 12	Part 2 Day 85	Day 6 to Day 127 of Part 2
Part 2 Week 24	Part 2 Day 169	Day 128 to Day 211 of Part 2
Part 2 Week 36	Part 2 Day 253	Day 212 to Day 295 of Part 2
Part 2 Week 48	Part 2 Day 337	Day 296 to Day 421 of Part 2
Part 2 Week 72	Part 2 Day 505	Day 422 to Day 589 of Part 2
Part 2 Week 96	Part 2 Day 673	Day 590 to Day 715 of Part 2
Part 2 Week 108	Part 2 Day 757	≥Day 716 of Part 2
NOTE: These assessments are measured every 12 weeks in Part 1. These assessments are measured every 12 weeks up to Part 2 Week 48 and then at Part 2 Week 72, Part 2 Week 96, Part 2 Week 108 in Part 2.		

12-Lead ECG		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Part 1		
Baseline	Day 1	Day 1 being the first day of dosing
Week 24	Day 169	Day 2 to Day 253
Week 48	Day 337	Day 254 to Day 421
Week 72	Day 505	Day 422 to Day 547
Week 84	Day 589	≥Day 548
Part 2		
Part 2 Day 1	Part 2 Day 1	Day -5 to Day 5 of Part 2
Part 2 Week 12	Part 2 Day 85	Day 6 to Day 127 of Part 2
Part 2 Week 24	Part 2 Day 169	Day 128 to Day 211 of Part 2
Part 2 Week 36	Part 2 Day 253	Day 212 to Day 295 of Part 2
Part 2 Week 48	Part 2 Day 337	Day 296 to Day 379 of Part 2
Part 2 Week 60	Part 2 Day 421	Day 380 to Day 463 of Part 2
Part 2 Week 72	Part 2 Day 505	Day 464 to Day 547 of Part 2
Part 2 Week 84	Part 2 Day 589	Day 548 to Day 631 of Part 2
Part 2 Week 96	Part 2 Day 673	Day 632 to Day 715 of Part 2
Part 2 Week 108	Part 2 Day 757	≥Day 716 of Part 2
NOTE: These assessments are measured every 24 weeks up to Week 72 and then at Week 84 in Part 1. These assessments are measured every 12 weeks in Part 2.		

C-SSRS		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Part 1		

Baseline	Day 1	Day 1 being the first day of dosing
Week 24	Day 169	Day 2 to Day 253
Week 48	Day 337	Day 254 to Day 421
Week 72	Day 505	Day 422 to Day 547
Week 84	Day 589	≥Day 548
Part 2		
Part 2 Day 1	Part 2 Day 1	Day -5 to Day 5 of Part 2
Part 2 Week 24	Part 2 Day 169	Day 6 to Day 253 of Part 2
Part 2 Week 48	Part 2 Day 337	Day 254 to Day 421 of Part 2
Part 2 Week 72	Part 2 Day 505	Day 422 to Day 589 of Part 2
Part 2 Week 96	Part 2 Day 673	Day 590 to Day 715 of Part 2
Part 2 Week 108	Part 2 Day 757	≥Day 716 of Part 2
NOTE: These assessments are measured every 24 weeks up to Week 72 and then at Week 84 in Part 1. These assessments are measured every 24 weeks up to Part 2 Week 96 and then at Part 2 Week 108 in Part 2.		

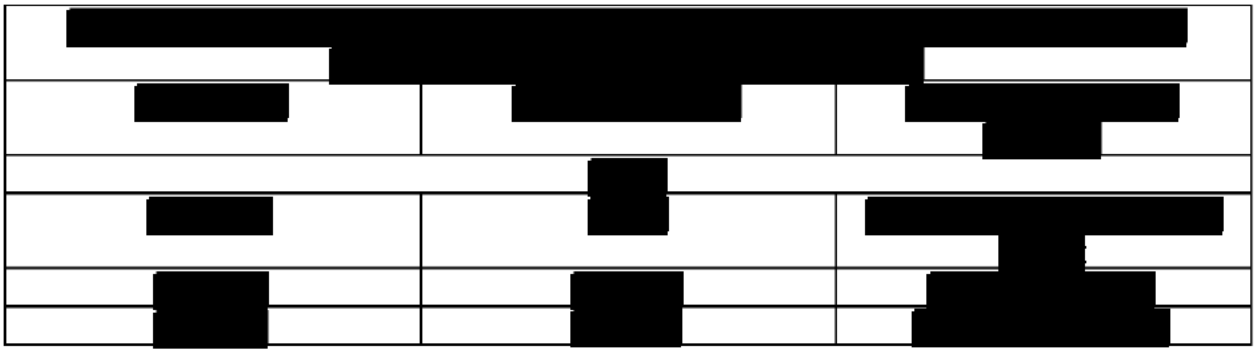
Vital Signs, Urine Pregnancy Test		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Part 1		
Baseline	Day 1	Day 1 being the first day of dosing
Week 4	Day 29	Day 2 to Day 43
Week 8	Day 57	Day 44 to Day 71
Week 12	Day 85	Day 72 to Day 99
Week 16	Day 113	Day 100 to Day 127
Week 20	Day 141	Day 128 to Day 155
Week 24	Day 169	Day 156 to Day 183
Week 28	Day 197	Day 184 to Day 211
Week 32	Day 225	Day 212 to Day 239
Week 36	Day 253	Day 240 to Day 267
Week 40	Day 281	Day 268 to Day 295
Week 44	Day 309	Day 296 to Day 323
Week 48	Day 337	Day 324 to Day 351
Week 52	Day 365	Day 352 to Day 379
Week 56	Day 393	Day 380 to Day 407
Week 60	Day 421	Day 408 to Day 435
Week 64	Day 449	Day 436 to Day 463
Week 68	Day 477	Day 464 to Day 491
Week 72	Day 505	Day 492 to Day 547
Week 84	Day 589	≥Day 548

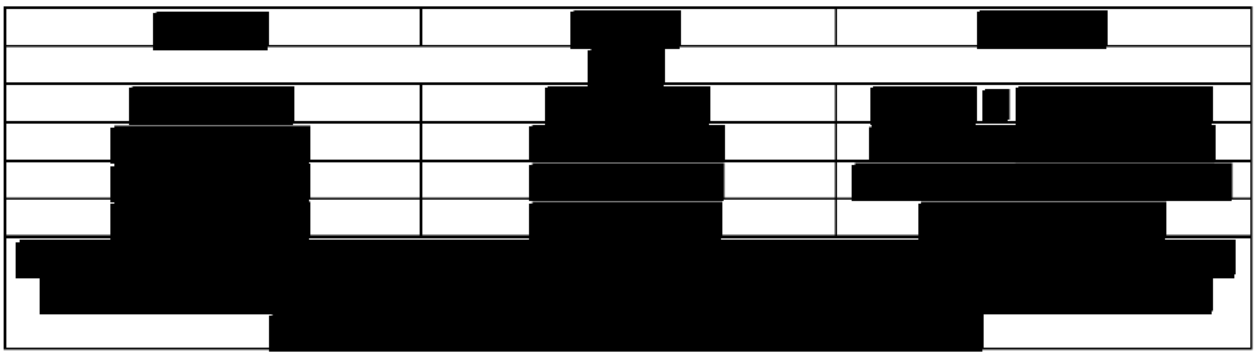
	Part 2	
Part 2 Day 1	Part 2 Day 1	Day -5 to Day 5 of Part 2
Part 2 Week 4	Part 2 Day 29	Day 6 to Day 43 of Part 2
Part 2 Week 8	Part 2 Day 57	Day 44 to Day 71 of Part 2
Part 2 Week 12	Part 2 Day 85	Day 72 to Day 99 of Part 2
Part 2 Week 16	Part 2 Day 113	Day 100 to Day 127 of Part 2
Part 2 Week 20	Part 2 Day 141	Day 128 to Day 155 of Part 2
Part 2 Week 24	Part 2 Day 169	Day 156 to Day 183 of Part 2
Part 2 Week 28	Part 2 Day 197	Day 184 to Day 211 of Part 2
Part 2 Week 32	Part 2 Day 225	Day 212 to Day 239 of Part 2
Part 2 Week 36	Part 2 Day 253	Day 240 to Day 267 of Part 2
Part 2 Week 40	Part 2 Day 281	Day 268 to Day 295 of Part 2
Part 2 Week 44	Part 2 Day 309	Day 296 to Day 323 of Part 2
Part 2 Week 48	Part 2 Day 337	Day 324 to Day 351 of Part 2
Part 2 Week 52	Part 2 Day 365	Day 352 to Day 379 of Part 2
Part 2 Week 56	Part 2 Day 393	Day 380 to Day 407 of Part 2
Part 2 Week 60	Part 2 Day 421	Day 408 to Day 435 of Part 2
Part 2 Week 64	Part 2 Day 449	Day 436 to Day 463 of Part 2
Part 2 Week 68	Part 2 Day 477	Day 464 to Day 491 of Part 2
Part 2 Week 72	Part 2 Day 505	Day 492 to Day 519 of Part 2
Part 2 Week 76	Part 2 Day 533	Day 520 to Day 547 of Part 2
Part 2 Week 80	Part 2 Day 561	Day 548 to Day 575 of Part 2
Part 2 Week 84	Part 2 Day 589	Day 576 to Day 603 of Part 2
Part 2 Week 88	Part 2 Day 617	Day 604 to Day 631 of Part 2
Part 2 Week 92	Part 2 Day 645	Day 632 to Day 659 of Part 2
Part 2 Week 96	Part 2 Day 673	Day 660 to Day 715 of Part 2
Part 2 Week 108	Part 2 Day 757	≥Day 716 of Part 2
NOTE: These assessments are measured every 4 weeks up to Week 72 and then at Week 84 in Part 1. These assessments are measured every 4 weeks up to Part 2 Week 96 and then at Part 2 Week 108 in Part 2.		

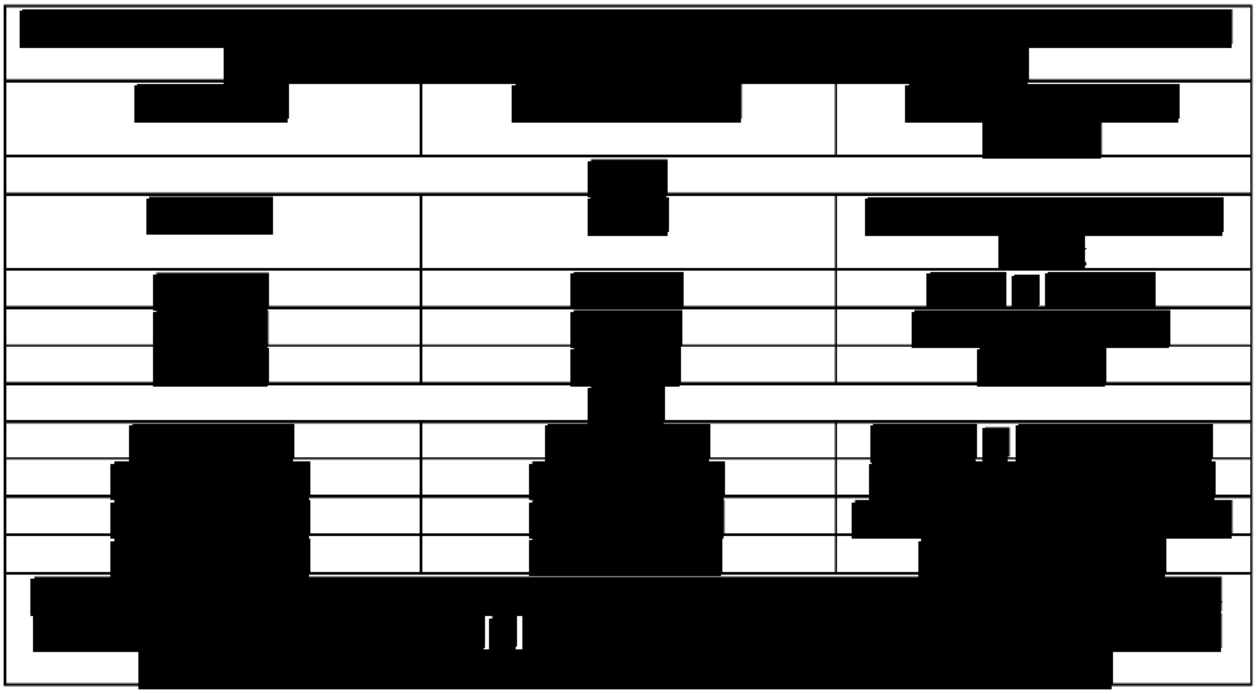
Hematology, Blood Chemistry and Urinalysis		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Part 1		
Baseline	Day 1	Day 1 being the first day of dosing
Week 4	Day 29	Day 2 to Day 43
Week 8	Day 57	Day 44 to Day 71
Week 12	Day 85	Day 72 to Day 99
Week 16	Day 113	Day 100 to Day 127
Week 20	Day 141	Day 128 to Day 155

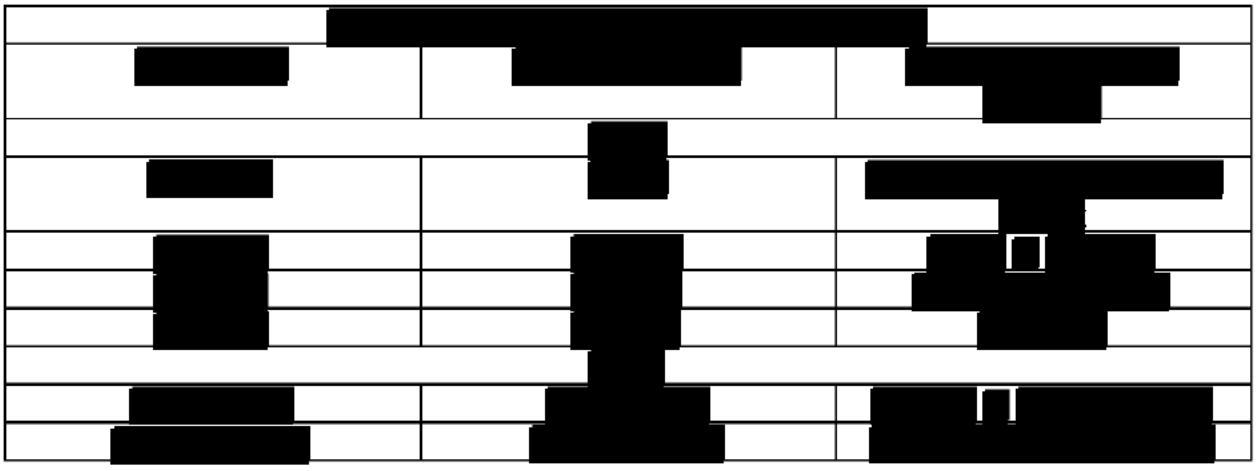
Week 24	Day 169	Day 156 to Day 211
Week 36	Day 253	Day 212 to Day 295
Week 48	Day 337	Day 296 to Day 379
Week 60	Day 421	Day 380 to Day 463
Week 72	Day 505	Day 464 to Day 547
Week 84	Day 589	≥Day 548
Part 2		
Part 2 Day 1	Part 2 Day 1	Day -5 to Day 5 of Part 2
Part 2 Week 12	Part 2 Day 85	Day 6 to Day 127 of Part 2
Part 2 Week 24	Part 2 Day 169	Day 128 to Day 211 of Part 2
Part 2 Week 36	Part 2 Day 253	Day 212 to Day 295 of Part 2
Part 2 Week 48	Part 2 Day 337	Day 296 to Day 379 of Part 2
Part 2 Week 60	Part 2 Day 421	Day 380 to Day 463 of Part 2
Part 2 Week 72	Part 2 Day 505	Day 464 to Day 547 of Part 2
Part 2 Week 84	Part 2 Day 589	Day 548 to Day 631 of Part 2
Part 2 Week 96	Part 2 Day 673	Day 632 to Day 715 of Part 2
Part 2 Week 108	Part 2 Day 757	≥Day 716 of Part 2
NOTE: These assessments are measured every 4 weeks before Week 24, and then every 12 weeks afterwards in Part 1. These assessments are measured every 12 weeks in Part 2.		

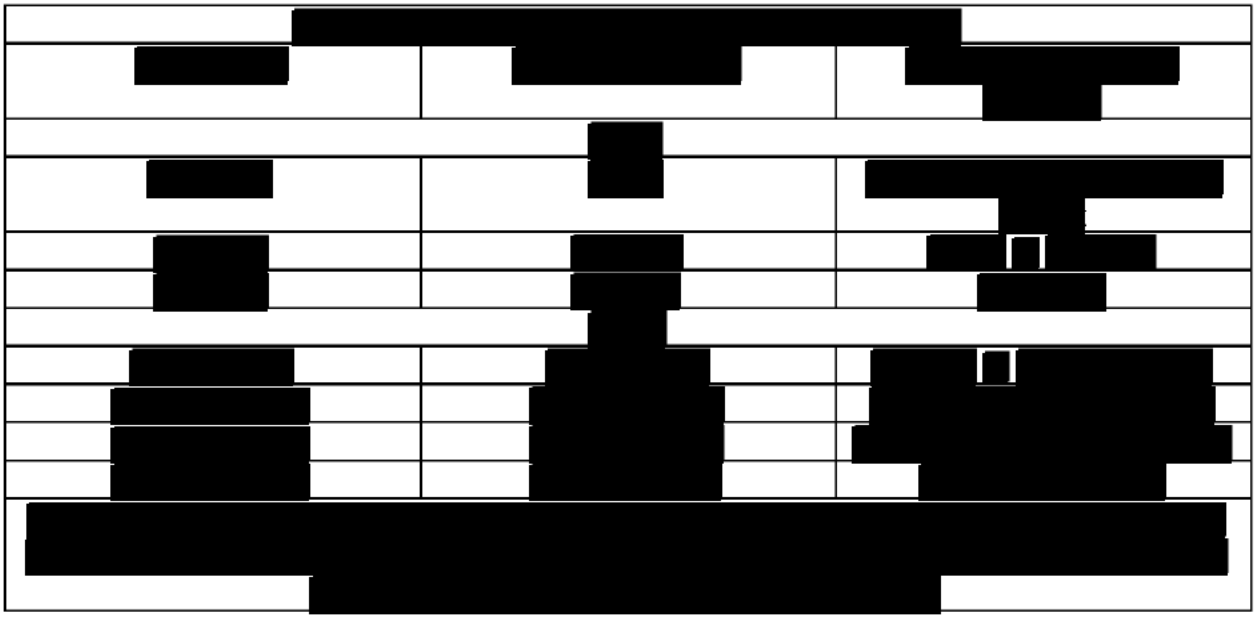
Blood Sample for Lipid Profile and Thyroid Tests		
Visit Name	**Target Visit Day**	**Study Day Range in Window**
Part 2		
Part 2 Day 1	Part 2 Day 1	Day -5 to Day 5 of Part 2
Part 2 Week 24	Part 2 Day 169	Day 6 to Day 253 of Part 2
Part 2 Week 48	Part 2 Day 337	Day 254 to Day 421 of Part 2
Part 2 Week 72	Part 2 Day 505	Day 422 to day 589 of Part 2
Part 2 Week 96	Part 2 Day 673	≥Day 590 of Part 2
NOTE: These assessments are not measured in Part 1. These assessments are measured every 24 weeks in Part 2.		

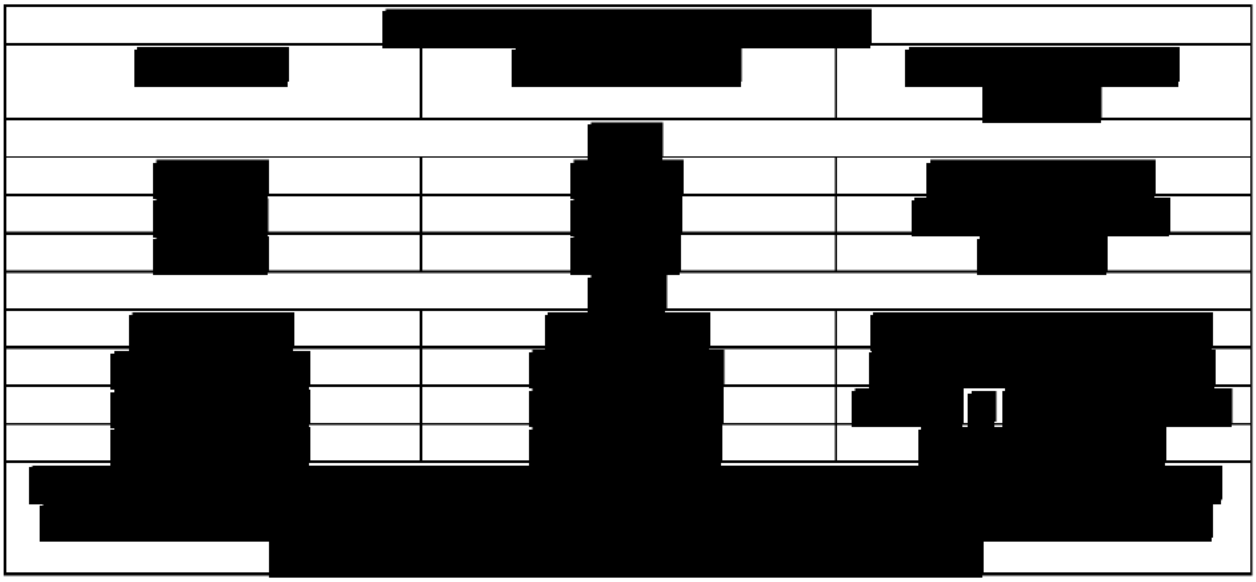


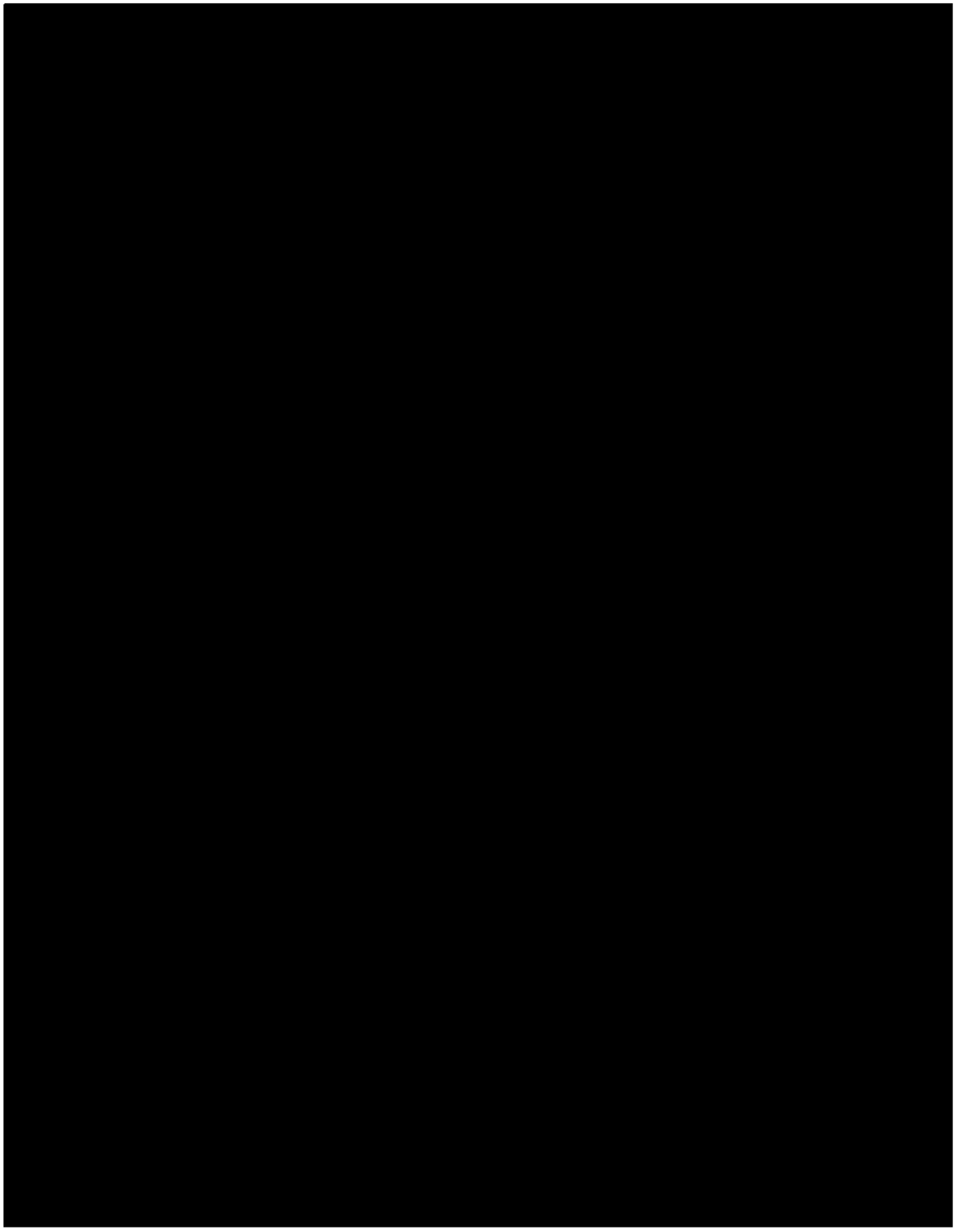


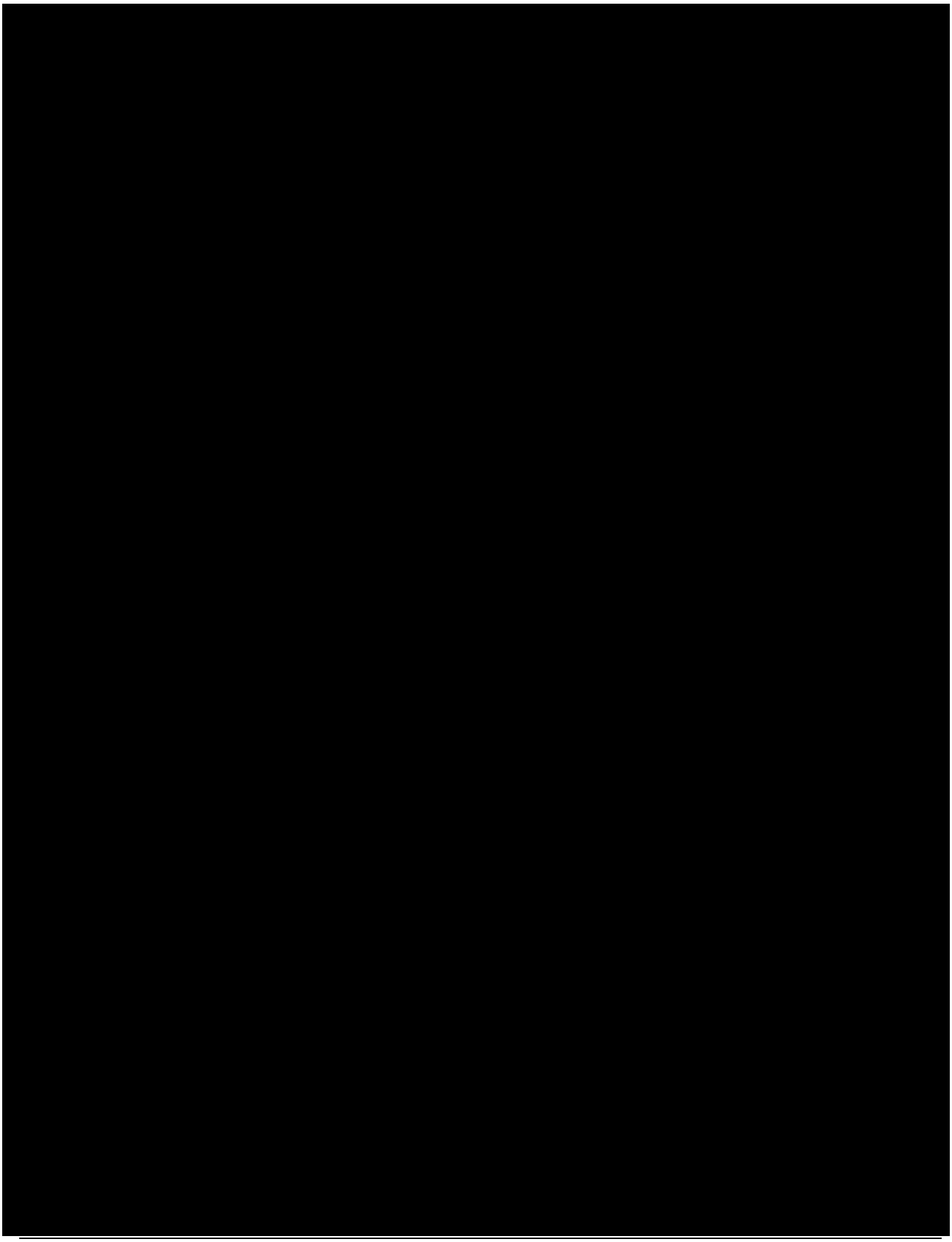


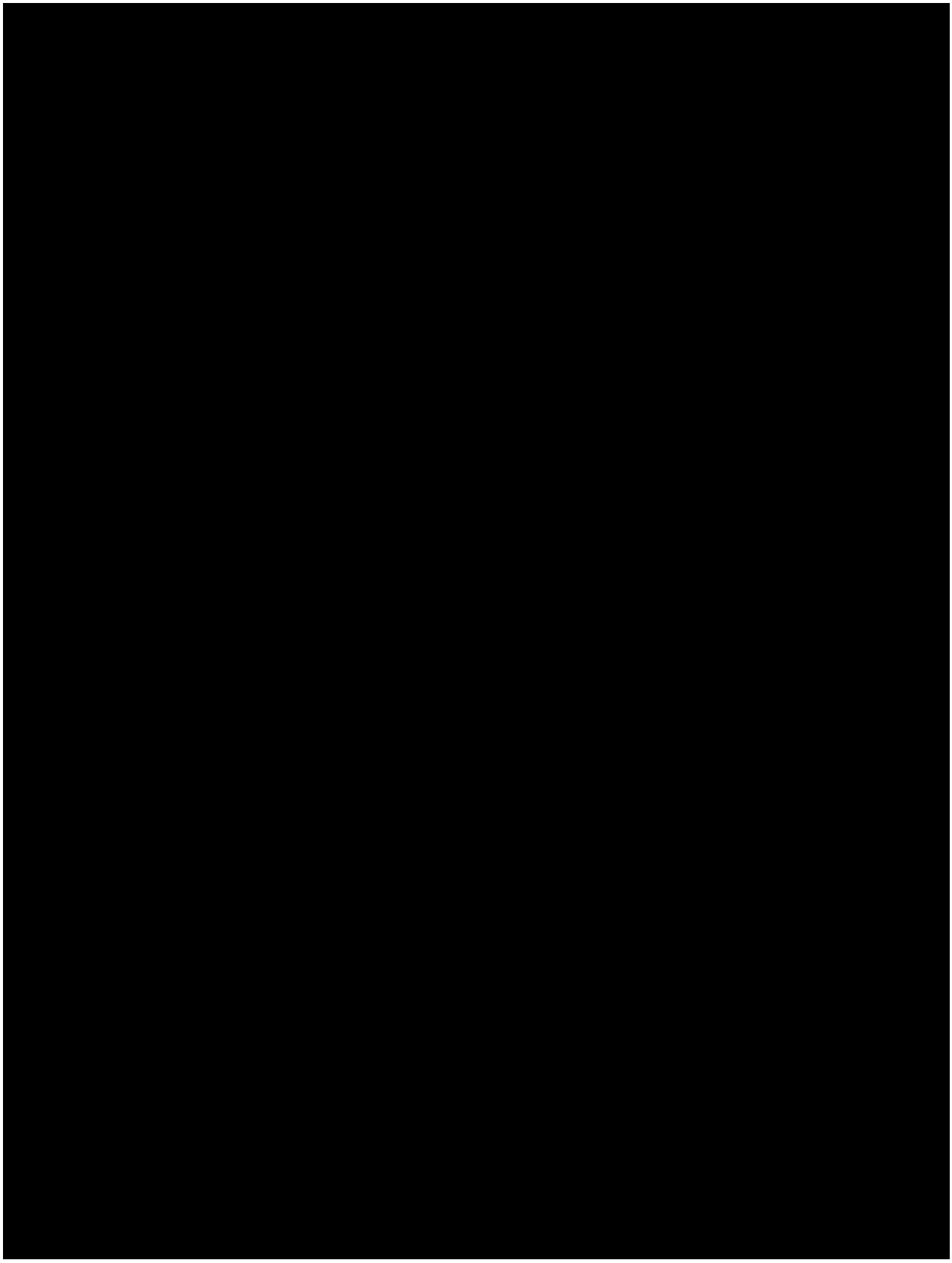


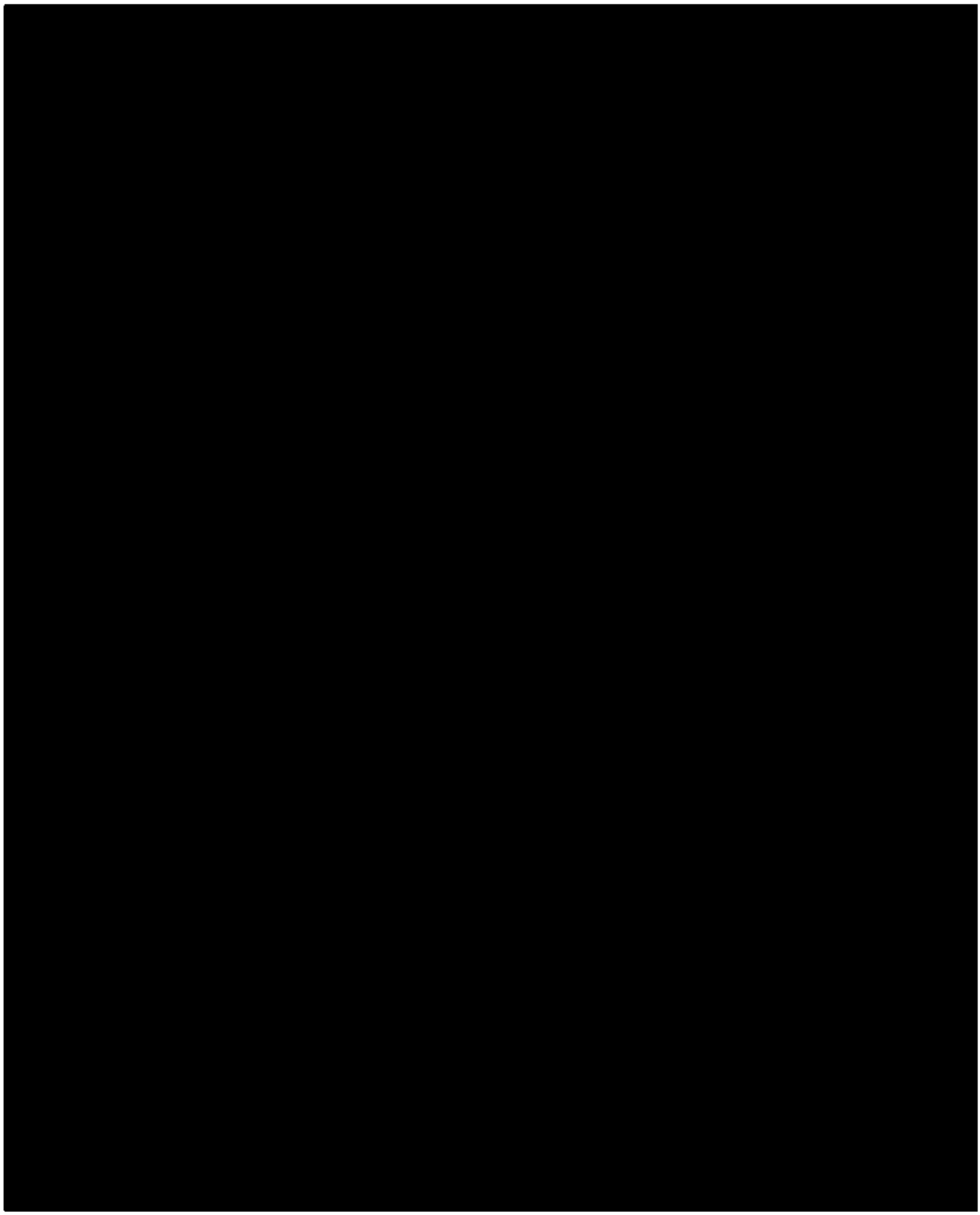












Appendix III Study Activities

Part 1 – Schedule of Activities

Table 7: Part 1 – Study Activities (Screening to Week 52)

Tests and Assessments[1]	Pretreatment	Treatment Period													
	Screening	Baseline	Visit Every 4 Weeks (±5 Days)												
Study Week (W) Day (D)	W -4 to D -1	W0 D1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52
Informed consent	X														
Eligibility criteria check	X	X													
Randomization		X													
Medical history and prior MS treatment	X	X													
Hepatitis B and C screen	X														
Physical examination	X	X[2]			X			X			X			X	
[redacted]															
T25FW, 9HPT-D, 9HPT-ND[4]	X	X			X			X			X			X	
[redacted]															
SDMT	X	X			X			X			X			X	
EDSS[5]	X	X			X			X			X			X	
PASAT-3	X	X			X			X			X			X	
MS signs and symptoms	X	X[2]			X			X			X			X	
Weight, height[6]	X	X[2]			X			X			X			X	
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X							X						X	
Hematology[8]	X	X[2]	X	X	X	X	X	X			X			X	
Blood chemistry	X	X[2]	X	X	X	X	X	X			X			X	

Tests and Assessments[1]	**Pretreatment**	**Treatment Period**													
	Screening	**Baseline**	**Visit Every 4 Weeks (±5 Days)**												
Study Week (W) **Day (D)**	**W -4 to D -1**	**W0** **D1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Urinalysis	X	X[2]	X	X	X	X	X	X			X			X	
Serum FSH[9]	X														
Serum pregnancy test[10]	X														
Urine pregnancy test[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															
Anti-BIIB033 Ab[13]		X	X		X			X						X	
[redacted]															
Practice tests[16]	X														
[redacted]															
BIIB033 or placebo IV infusion[19]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS		X						X						X	
AEs			□----------AE monitoring from study treatment dosing through to EOS----------□												
SAEs	□----------SAE monitoring from signing of ICF through to EOS----------□														
Concomitant therapy	□----------Concomitant therapy monitoring from signing of ICF through to EOS----------□														

9HPT-D,-ND=9-Hole Peg Test (dominant hand, nondominant hand); Ab=antibody; AE=adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; [redacted]; ECG=electrocardiogram; eCRF=electronic case report form; EDSS=Expanded Disability Status Scale; EMS=Early Multiple Sclerosis; EOS=End of Study; ET=Early Termination; FSH = follicle-stimulating hormone; [redacted]; ICF=Informed Consent Form; IV=intravenous; [redacted]; MS=multiple sclerosis; [redacted]; PASAT-3=3-Second Paced Auditory Serial Addition Test; [redacted]; PT=prothrombin time; PTT=partial thromboplastin time; [redacted] SAE=serious adverse event; SDMT=Symbol-Digit Modalities Test; T25FW=Timed 25-Foot Walk.

Note: See **Table 8** for other study visits, including Unscheduled Visit for Relapse Assessment and ET and EOS Visits.

[1] Tests and assessments should be performed in the order listed, where possible. It is not required that all Screening tests and assessments be completed during 1 pretreatment visit.
[2] If a Screening test is performed within 7 days of Day 1/Baseline, the assessments do not need to be repeated at Day 1/Baseline.
[redacted]
[4] At each visit, T25FW, 9HPT-D, and 9HPT-ND must be tested twice each. Tests should be performed in the following order where possible: T25FW, 9HPT-D, 9HPT-ND, [redacted] and SDMT before EDSS.
[5] EDSS score is required to be stable between Screening and Day 1/Baseline Visits. Refer to the Study Reference Guide for additional instructions.
[6] Height will be measured at Screening only.
[7] Include temperature, blood pressure, pulse rate, and respiratory rate (after being seated for at least 5 minutes).
[8] PT, PTT, and platelets will also be measured for all subjects at Screening.
[9] Required for postmenopausal female subjects only.
[10] For females of child-bearing potential. Results must be known prior to Day 1/Baseline.
[11] For females of child-bearing potential. Results must be known prior to each study treatment administration.
[redacted]
[13] Predose samples (sample should be taken within 1 hour prior to study treatment dosing if possible) on Day 1/Baseline and at Weeks 4,12, 24, 48, and 72 and EOS/ET. Exact collection times will be recorded in the eCRF.
[redacted]
[16] Subjects should perform a separate practice test for T25FW, 9HPT-D, 9HPT-ND, and PASAT-3 at their Screening Visit. T25FW, 9HPT-D, and 9HPT-ND should be performed twice. The Screening and practice tests on these measurements should be separated by at least 1 hour. The Screening and Baseline tests on these measurements should be separated by at least 5 days.
[redacted]
[19] For subjects on natalizumab (Tysabri), natalizumab infusions and study treatment infusions may be on the same day; however, natalizumab should be administered prior to study treatment (BIIB033 or placebo) if given on that same day, with a minimum 1-hour interval between infusions. If any infusion reaction occurs with natalizumab, the infusion of BIIB033 should not be administered on that same day.

Table 8: Part 1 – Study Activities (Week 56 to Week 84)

	Treatment Period							Follow-Up
Tests and Assessments[1]	**Visit Every 4 Weeks (±5 Days)**					**Unscheduled Visit for Relapse Assessment[2] (Within 5 Days of the Onset)**	**ET[3]**	**EOS[4]**
Study Week (W)	**W56**	**W60**	**W64**	**W68**	**W72[5]**			**W84 ± 10 days**
Informed consent for Part 2[6]					X			
Eligibility criteria check for Part 2					X			
Physical examination		X			X	X	X	X
[redacted]								
T25FW, 9HPT-D, 9HPT-ND[8]		X			X	X[9]	X	X
[redacted]								
SDMT		X			X	X[9]	X	X
EDSS		X			X	X[9]	X	X
PASAT-3		X			X	X[9]	X	X
MS signs and symptoms		X			X	X	X	X
Weight		X			X	X	X	X
Vital signs[10]	X	X	X	X	X	X	X	X
12-Lead ECG					X		X	X
Hematology		X			X	X[11]	X	X
Blood chemistry		X			X	X[11]	X	X
Urinalysis		X			X	X[11]	X	X
Urine pregnancy test[12]	X	X	X	X	X		X	X

	Treatment Period							Follow-Up
Tests and Assessments[1]	**Visit Every 4 Weeks (±5 Days)**					**Unscheduled Visit for Relapse Assessment[2] (Within 5 Days of the Onset)**	**ET[3]**	**EOS[4]**
Study Week (W)	**W56**	**W60**	**W64**	**W68**	**W72[5]**			**W84 ± 10 days**
[redacted]								
Anti-BIIB033 Ab[14]					X		X	X
[redacted]								
BIIB033 or placebo IV infusion[19]	X	X	X	X	X			
C-SSRS					X		X	X
AEs	□----------AE monitoring from study treatment dosing through to EOS----------□							
SAEs	□----------SAE monitoring from signing of ICF through to EOS----------□							
Concomitant therapy	□----------Concomitant therapy monitoring from signing of ICF through to EOS----------□							

9HPT-D, -ND=9-Hole Peg Test (dominant hand, nondominant hand); Ab=antibody; AE=adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; eCRF=electronic case report form; EDSS=Expanded Disability Status Scale; EMS=Early Multiple Sclerosis; EOS=End of Study; ET=Early Termination; [redacted]; ICF=Informed Consent Form; IV=intravenous; [redacted]; PASAT-3=3-Second Paced Auditory Serial Addition Test; [redacted]; SAE=serious adverse event; SDMT=Symbol-Digit Modalities Test; [redacted]; T25FW=Timed 25-Foot Walk.

1 Tests and assessments should be performed in the order listed where possible.

2 If a suspected MS relapse occurs during the study, the subject should return to the study site within 5 days after onset of the event for evaluation. Unscheduled visits to be determined at the discretion of the Investigator for nonsuspected relapses.

3 In the event that a subject withdraws from the study prematurely, an ET visit should be performed as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS study visit 12 weeks (±10 days) after the final dose of study treatment; all EOS assessments listed in the study schedule should be performed at this EOS visit.

4 For subjects not participating in Part 2, EOS visit occurs at 12 weeks (±10 days) after administration of the last dose of study treatment.

5 For subjects participating in Part 2, Week 72 will be the combined final Part 1 Visit and the Part 2 Screening Visit (see **Part 2 – Schedule of Activities Table 9**).

6 Informed consent for the optional substudy is obtained at Week 72 for subjects participating in Part 2.

[redacted]

8 At each visit, T25FW, 9HPT-D, and 9HPT-ND must be tested twice each. Tests should be performed in the following order where possible: T25FW, 9HPT-D, 9HPT-ND, [redacted] and SDMT before EDSS

9 EDSS, T25FW, 9HPT, LCVA, SDMT, and PASAT-3 should only be assessed at an unscheduled visit if relapse is suspected. Refer to the Study Reference Guide for additional instructions.

10 Include temperature, blood pressure, pulse rate, and respiratory rate (after being seated for at least 5 minutes).

11 To be performed only at the discretion of the treating physician if infection or metabolic disturbance is suspected to be contributing to the unscheduled visit.

12 For females of child-bearing potential. Results must be known prior to each study treatment administration.

[redacted]

14 Predose samples (sample should be taken within 1 hour prior to study treatment dosing if possible) on Day 1/Baseline and at Weeks 4,12, 24, 48, and 72 and EOS/ET. Exact collection times will be recorded in the eCRF.

[redacted]

19 For subjects on natalizumab (Tysabri), natalizumab infusions and study treatment infusions may be on the same day; however, natalizumab should be administered prior to study treatment (BIIB033 or placebo) if given on that same day, with a minimum 1-hour interval between infusions. If any infusion reaction occurs with natalizumab, the infusion of BIIB033 should not be administered on that same day.

Part 2 – Schedule of Activities

Table 9: Part 2 – Study Activities (Screening to Week 52)

Tests and Assessments[1]		**Treatment Period**													
	Screening[2]	**Part 2/Day 1**[3]	**Visit Every 4 Weeks (±5 Days)**												
Study Week (W) Day (D)	**W -4 to D -1**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Informed consent[4]	X	X													
Eligibility criteria check	X	X													
Physical examination	X	X						X						X	
[redacted]															
T25FW, 9HPT-D, 9HPT-ND[6]		X						X						X	
[redacted]															
SDMT		X						X						X	
[redacted]															
EDSS		X						X						X	
PASAT-3		X						X						X	
MS signs and symptoms	X	X						X						X	
Weight, height[8]	X	X			X			X			X			X	
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X			X			X			X			X	
Hematology[10]	X	X			X			X			X			X	
Blood chemistry	X	X			X			X			X			X	
Urinalysis	X	X			X			X			X			X	
Urine pregnancy test[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															

Tests and Assessments[1]		**Treatment Period**													
	Screening[2]	**Part 2/Day 1**[3]	**Visit Every 4 Weeks (±5 Days)**												
Study Week (W) Day (D)	**W -4 to D -1**	**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Blood Sample for Anti-BIIB033 Ab[12]		X						X						X	
Blood sample for lipid profile and thyroid tests		X						X						X	
[redacted]															
BIIB033 IV infusion[18]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X						X						X	
[redacted]															
AEs	←----------AE monitoring from signing of the ICF through to EOS----------→														
SAEs	←----------SAE monitoring from signing of ICF through to EOS----------→														
Concomitant therapy	←----------Concomitant therapy monitoring from signing of ICF through to EOS----------→														

[redacted]; 9HPT-D,-ND=9-Hole Peg Test (dominant hand, nondominant hand); Ab=antibody; ADL=Activities of Daily Living-Cognitive and Instrumental; AE=adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; D = Day; [redacted]; ECG=electrocardiogram; eCRF=electronic case report form; EDSS=Expanded Disability Status Scale; EMS=Early Multiple Sclerosis; EOS=End of Study; ET=Early Termination; FSH = follicle-stimulating hormone; [redacted] ICF=Informed Consent Form; IV=intravenous; [redacted]; MS=multiple sclerosis; [redacted] PASAT-3=3-Second Paced Auditory Serial Addition Test; [redacted]; PT=prothrombin time; PTT=partial thromboplastin time; [redacted]; SAE=serious adverse event; SDMT=Symbol-Digit Modalities Test; T25FW=Timed 25-Foot Walk; W = Week

[1] Test and assessment should be performed in the order listed where possible.

[2] Screening Visit should be performed as part of Part 1/Week 72 Visit. In case the Part 2 Screening Visit is unable to be performed at Part 1/Week 72, a separate Screening Visit may occur within 4 weeks of Part 2/Day 1. Any test/assessment done within 28 days prior to Part 2/Day 1 will be used for screening for Part 2 and does not need to be repeated.

[3] When possible, the Part 2/Day 1 should be performed 4 weeks from the Part 1/Week 72 Visit. If not possible in 4 weeks, the maximum window is 12 weeks from Part 1/Week 72, and the patients should roll over into Part 2 as soon as possible within weeks 4 to 12.
[4] Informed consent for the optional substudy should also be obtained on Part 2/Day 1 before the substudy procedures.

[redacted]

[6] At each visit, T25FW, 9HPT-D, and 9HPT-ND must be tested twice each. Tests should be performed in the following order where possible: T25FW, 9HPT-D, 9HPT ND, [redacted], SDMT, 6MWT, and then EDSS.

[redacted]

[8] Height at Part 2/Day 1 only.
[9] Includes temperature, blood pressure, pulse rate, and respiratory rate (after being seated for at least 5 minutes).
[10] PT, PTT, and platelets will also be measured for all subjects on Part 2/Day 1 and at each visit when hematology is done.
[11] For females of child-bearing potential. Results must be known prior to each study treatment administration.
[12] The period between predose sample collection and administering of the study treatment should not exceed 24 hours, and the exact time and date at which the sample was collected should be recorded in the eCRF.

[redacted]

Table 10: Part 2 – Study Activities (Week 56 to Week 96)

Tests and Assessments[1]	**Treatment Period**													**Follow Up**
	Visit Every 4 Weeks (±5 Days)											**Unscheduled Visit for Relapse Assessment**[2] **(Within 5 Days of the Onset)**	**ET**[3]	**EOS**[4]
Study Week (W)	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**			**W108± 10d**
Physical examination					X						X	X	X	X
[redacted]														
T25FW, 9HPT-D, 9HPT-ND[6]					X						X	X[6]	X	X
[redacted]														
SDMT					X						X	X[6]	X	X
[redacted]														
EDSS					X						X	X[6]	X	X
PASAT-3					X						X	X[6]	X	X
MS signs and symptoms					X						X	X	X	X
Weight					X						X	X	X	X
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG		X			X			X			X		X	X
Hematology		X			X			X			X	X[9]	X	X

Tests and Assessments[1]	**Treatment Period**													**Follow Up**
	Visit Every 4 Weeks (±5 Days)											**Unscheduled Visit for Relapse Assessment**[2] **(Within 5 Days of the Onset)**	**ET**[3]	**EOS**[4]
Study Week (W)	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**			**W108± 10d**
Blood chemistry		X			X			X			X	X[10]	X	X
Urinalysis		X			X			X			X	X[11]	X	X
Urine pregnancy test[12]	X	X	X	X	X	X	X	X	X	X	X		X	X
[redacted]														
Blood sample for Anti-BIIB033 Ab[11]					X						X		X	X
Blood sample for lipid profile and thyroid tests					X						X			
[redacted]														

Tests and Assessments[1]	**Treatment Period**													**Follow Up**
	Visit Every 4 Weeks (±5 Days)											**Unscheduled Visit for Relapse Assessment**[2] **(Within 5 Days of the Onset)**	**ET**[3]	**EOS**[4]
Study Week (W)	**W56**	**W60**	**W64**	**W68**	**W72**	**W76**	**W80**	**W84**	**W88**	**W92**	**W96**			**W108± 10d**
[redacted]														
BIIB033 IV infusion[16]	X	X	X	X	X	X	X	X	X	X	X			
C-SSRS					X[17]						X		X	X
[redacted]														
AEs	←----------AE monitoring from signing of Part 2 ICF through to EOS----------→													
SAEs	←----------SAE monitoring from signing of Part 2 ICF through to EOS----------→													
Concomitant therapy	←----------Concomitant therapy monitoring from signing of Part 2 ICF through to EOS----------→													

[redacted]; 9HPT-D, -ND=9-Hole Peg Test (dominant hand, nondominant hand); Ab=antibody; ADL=Activities of Daily Living-Cognitive and Instrumental; AE=adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; eCRF=electronic case report form; [redacted]; EDSS=Expanded Disability Status Scale; EMS=Early Multiple Sclerosis; EOS=End of Study; ET=Early Termination; hbA1C = glycated hemoglobin; [redacted]; ICF=Informed Consent Form; IV=intravenous; [redacted]; mmEP = multi-modal evoked potential; [redacted]; PASAT-3=3-Second Paced Auditory Serial Addition Test; [redacted]; SAE=serious adverse event; SDMT=Symbol-Digit Modalities Test; T25FW=Timed 25-Foot Walk; W = Week

[1] Tests and assessments should be performed in the order listed where possible.

[2] If a suspected MS relapse occurs during the study, the subject should return to the study site within 5 days after onset of the event for evaluation. Unscheduled visits to be determined at the discretion of the Investigator for nonsuspected relapses.

[3] In the event that a subject withdraws from the study prematurely, an ET Visit should be performed as soon as possible but no later than 4 weeks after the last dose of study treatment.

[4] EOS Visit occurs at 12 weeks (±10 days) after administration of the last dose of study treatment. All EOS assessments listed in the study schedule should be performed at this EOS Visit.

[redacted]

[6] At each visit, T25FW, 9HPT-D, and 9HPT-ND must be tested twice each. Tests should be performed in the following order where possible: T25FW, 9HPT-D, 9HPT-ND, [redacted] SDMT, 6MWT, and then EDSS.

[redacted]

[8] Includes temperature, blood pressure, pulse rate, and respiratory rate (after being seated for at least 5 minutes).
[9] To be performed only at the discretion of the treating physician if infection or metabolic disturbance is suspected to be contributing to the unscheduled visit.
[10] For females of child-bearing potential. Results must be known prior to each study treatment administration.
[11] The period between predose sample collection and administering of the study treatment should not exceed 24 hours, and the exact time and date at which the sample was collected should be recorded in the eCRF.
[12] Biomarker and RNA samples will be collected at the time of predose PK sampling.

[redacted]

[16] For subjects on natalizumab (Tysabri), natalizumab infusions and study treatment infusions may be on the same day; however, natalizumab should be administered prior to study treatment (BIIB033 or placebo) if given on that same day, with a minimum 1-hour interval between infusions. If any infusion reaction occurs with natalizumab, the infusion of BIIB033 should not be administered on that same day.

[redacted]