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PROTOCOL NUMBER: 215MS202/NCT03222973

PHASE OF DEVELOPMENT: 2

PROTOCOL 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

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Protocol 215MS202 was approved by:

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[redacted]

Biogen

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1. SYNOPSIS

Protocol 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
Protocol Number	215MS202
Version Number	3
Name of Study Treatment	BIIB033; opicinumab
Study Phase	2
Study Indication	Multiple Sclerosis (MS)
Study Rationale	The objective of this study is to evaluate the efficacy and safety of BIIB033 used as add-on therapy to anti-inflammatory disease-modifying therapies (DMTs) in subjects with relapsing multiple sclerosis (RMS). BIIB033 is a first-in-class human monoclonal antibody directed against LINGO-1, a negative regulator of oligodendrocyte progenitor cells (OPCs) differentiation and myelination. The therapeutic hypothesis is that BIIB033 will act in the central nervous system (CNS) to block LINGO-1, which is expressed on both oligodendrocytes and neurons. In turn, the inhibition of LINGO-1 may promote remyelination via differentiation of OPCs normally present in the CNS and promote axonal regeneration by blocking signaling from myelin debris on the Nogo66 receptor 1 complex in neurons. Therefore, BIIB033 treatment in demyelinating diseases such as MS may lead to improved CNS repair with corresponding beneficial effects on neurological function and disability. Three Phase 1 studies and 2 Phase 2 studies evaluating BIIB033 have been completed. Study 215ON201 was a 24-week, randomized, Phase 2 study of BIIB033 (100 mg/kg intravenous [IV] every 4 weeks) versus placebo in 82 subjects with acute optic neuritis. Proof of biology was achieved as shown by an improvement in the latency of visual evoked potentials. Study 215MS201 was a 72-week, placebo-controlled, Phase 2, dose-ranging study of BIIB033 (range 3 to 100 mg/kg IV every 4 weeks) as add-on therapy to interferon beta (IFNβ) [Avonex®] in 419

subjects with RMS. The primary endpoint was confirmed improvement in 1 or more assessments of a multicomponent disability endpoint over 72 weeks. A statistically significant linear dose-response on primary endpoint was not observed with BIIB033 treatment versus placebo (p=0.9831). Analyses showed a non-monotonic, inverted U-shaped dose response to BIIB033, with more favorable outcomes in the 10- and 30-mg/kg groups. Prespecified univariate subgroup analyses showed that, in general, younger subjects and those with clinical [redacted] features suggestive of more preserved brain tissue integrity tended to respond better to BIIB033 treatment.

[redacted]

BIIB033 was generally well tolerated across both Phase 2 studies (215ON201 and 215MS201). Hypersensitivity reactions occurred in 2 subjects (5% of BIIB033-treated subjects) in Study 215ON201 and 4 subjects (1% of BIIB033-treated subjects) in Study 215MS201; in both studies, the hypersensitivity reactions occurred at the 100-mg/kg dose. Postbaseline weight gain was also observed in both Phase 2 studies. In Study 215MS201, there was a trend for dose-dependent weight gain over 72 weeks, with a mean increase between 0.9 and 1.9 kg in the 4 BIIB033 dosing groups. The mechanism of the weight gain is not known at this time.

The proposed study (215MS202) has 2 parts:

- Part 1 will further investigate the efficacy and safety of BIIB033 as an add-on therapy in subjects with RMS who are on a stable dose of an anti-inflammatory DMT and with baseline characteristics consistent with projected enhanced treatment effect of BIIB033 as identified in the post hoc analysis from Study 215MS201.

- The optional open-label extension (OLE) study (Part 2) will investigate the long-term safety and efficacy of BIIB033 treatment as an add-on therapy to anti-inflammatory DMTs for approximately 2 years (96 weeks). [redacted]

[redacted]

Study Objectives and Endpoints

Part 1

The primary objective of Part 1 of the study is to evaluate the effects of BIIB033 versus placebo on disability improvement over 72 weeks.

The primary endpoint that relates to this objective is the Overall Response Score, assessed over 72 weeks of the study.

The Overall Response Score is a multicomponent score based on 4 components: Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), 9-Hole Peg Test in the dominant hand (9HPT-D), and 9HPT in the nondominant hand (9HPT-ND). It assesses the overall change in disability over time. Score ranges from +4 to -4. At each visit, each component is given a score relative to baseline: -1 (if threshold is met for worsening), 0 (no changes meet threshold criteria), or +1 (if threshold is met for improvement). The thresholds for T25FW, 9HPT-D, and 9HPT-ND are defined by a 15% change from baseline (i.e., ≥15% decrease from baseline for improvement and ≥15% increase from baseline for worsening). For EDSS, improvement is defined as a ≥1.0-point decrease in EDSS from a baseline score of ≤6.0, and worsening is defined as a ≥1-point increase from a baseline score of ≤5.5 or a ≥0.5-point increase from a baseline score equal to 6.0.

The secondary objective and corresponding endpoints for Part 1 of the study are as follows:

- To evaluate the effects of BIIB033 versus placebo on additional measures of disability improvement
  - Proportion of subjects with 12-week confirmed improvement (as defined above) in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND
  - Proportion of subjects with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, or 3-Second Paced Auditory Serial Addition Test (PASAT-3) [improvement in PASAT-3 is defined as a ≥15% increase from baseline]
  - Proportion of subjects with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND, and without

confirmed worsening in any of the 4 assessments during the 72 weeks of the study

- Proportion of subjects with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and Symbol Digit Modalities Test (SDMT) [improvement in SDMT is defined as a ≥4-point increase from baseline]

- Proportion of subjects with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND (20% thresholds for T25FW and 9HPT)

Part 2

(Note: The BIIB033 Treatment Baseline in Part 2 is defined as the timepoint when the first dose of BIIB033 was given, i.e., Part 1/Day 1 for subjects treated with BIIB033 in Part 1, and as Part 2/Day 1 for subjects treated with placebo in Part 1.)

The primary objective of Part 2 is to evaluate the long-term safety profile of BIIB033 as an add-on therapy in subjects with MS.

The primary endpoint in Part 2 of the study that relates to this objective is as follows:

- Incidence of AEs and SAEs over 96 weeks in Part 2

The secondary objective of Part 2 is to investigate long-term efficacy (disability improvement) and additional safety measures of BIIB033 as an add-on therapy in subjects with MS.

The endpoints supporting the secondary objective are as follows:

- Overall Response Score over 96 weeks in Part 2

- Proportion of subjects with 24-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND (improvement in T25FW and 9HPT is defined as a ≥15% decrease from the BIIB033 Treatment Baseline)

- Proportion of subjects with 24-week confirmed improvement 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 the BIIB033 Treatment Baseline)

- Proportion of subjects with 24-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and without confirmed worsening in any of the 4 assessments during the 96 weeks of the study
- Proportion of subjects with 24-week confirmed improvement 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 the BIIB033 Treatment Baseline)
- Proportion of subjects with 24-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 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
- Columbia Suicide Severity Rating Scale (C-SSRS) over 96 weeks in Part 2

[redacted]

Study Design: **Part 1**

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.

Subjects enrolled must have been treated for at least 24 consecutive weeks prior to Day 1/Baseline on an anti-inflammatory DMT from 1 of the following 3 groups: IFNβ (Avonex, Plegridy®, Betaferon®/Betaseron®, or Rebif®), dimethyl fumarate (DMF; Tecfidera®), or natalizumab (Tysabri®). Subjects will continue taking their DMT throughout the study. Treating neurologists will manage DMT treatment for each subject.

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.

Part 2

Subjects who have completed study treatment (BIIB033 or placebo) in Part 1 will have the option to take part in Part 2, which is a 96-week multicenter, OLE phase that will evaluate BIIB033-treated subjects for long-term safety and efficacy of BIIB033 treatment, [redacted]. Subjects will continue the anti-inflammatory DMT used at the end of Part 1. DMT treatment in Part 2 will continue to be managed by the Investigator. The study will include clinical assessments every 24 weeks [redacted].

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

Study Location:

Part 1: Approximately 150 sites in 15 countries are planned.

Part 2: Approximately 95 sites in 15 countries are planned.

Number of Planned Subjects:

Part 1

Approximately 240 subjects will be enrolled, with approximately 120 subjects per treatment group (BIIB033; placebo).

Subjects will be stratified by MS type (relapsing-remitting multiple sclerosis [RRMS] versus secondary progressive multiple sclerosis [SPMS]), background DMT group, [redacted].

Part 2

All subjects who have completed study treatment through Week 72 in Part 1 and have consented and are eligible to participate in Part 2 of the study will be enrolled. [redacted]

Study Population:

Part 1

Eligible subjects are required to be between the ages of 18 and 58 years, inclusive, with a baseline EDSS of 2.0 to 6.0, have a diagnosis of RRMS per the 2010 McDonald's criteria [Polman 2011] or onset of SPMS per the Lublin and Reingold criteria [Lublin 2014], and

should have experienced their first MS symptom(s) within the previous 20 years.

Subjects must have experienced at least 1 of the following within 24 months prior to Day 1/Baseline: a clinical relapse (but not within 24 weeks prior to Day 1/Baseline), [redacted]

Subjects must be on a stable dose of a protocol-specified anti-inflammatory DMT (IFNβ [Avonex, Plegridy, Betaferon/Betaseron, or Rebif], DMF [Tecfidera], or natalizumab [Tysabri]) for at least 24 weeks prior to enrollment.

[redacted]

Part 2

Subjects who have completed treatment with BIIB033 or placebo in Part 1, and who have consented and are eligible to participate in Part 2 of the study will be enrolled. Subjects enrolling in Part 2 must meet the Part 2 criteria detailed in Section 8.3 and Section 8.4. Subjects will continue the DMT used at the end of Part 1. [redacted]

Treatment Groups: **Part 1**

Eligible subjects will be randomized in a 1:1 ratio into 2 parallel treatment groups: IV infusions of 750 mg BIIB033 or placebo every 4 weeks.

The study treatments will be given as add-on therapy to subjects already stable for at least 24 consecutive weeks on a protocol-defined anti-inflammatory DMT.

Part 2

All subjects will receive IV infusions of open-label BIIB033 750 mg once every 4 weeks as an add-on therapy to anti-inflammatory DMT.

Duration of Treatment and Follow-up:	**Part 1** Study duration will be approximately 88 weeks for subjects participating in Part 1 only: • 4-week Screening Period • 72-week Treatment Period • 12-week Follow-up Period Subjects who enroll in Part 2 do not need to have the 12-week postdose follow-up (End of Study), so the study duration in Part 1 will be approximately 76 weeks. **Part 2** The duration of Part 2 will be approximately 112 weeks: • 4-week Screening Period • 96-week Treatment Period • 12-week Follow-up Period Total study duration for subjects who participate in both Part 1 and Part 2 will be approximately 188 weeks.

2. LIST OF ABBREVIATIONS

4-AP	4-aminopyridine
[redacted]	[redacted]
9HPT-D, ND	9-Hole Peg Test (dominant hand, nondominant hand)
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamate pyruvate transaminase
AON	acute optic neuritis
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
C_{max}	maximum observed concentration
CNS	central nervous system
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DHA	Directions for Handling and Administration
ADL	Activities of Daily Living-Cognitive and Instrumental
DMF	dimethyl fumarate
DMT	disease-modifying therapy
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
EMS	Early Multiple Sclerosis
EOS	End of Study
ET	Early Termination
FT4	free thyroxine
GA	glatiramer acetate
GCP	Good Clinical Practice
[redacted]	[redacted]
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IFNβ	interferon beta
IgG_1	immunoglobulin G subclass 1
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
[redacted]	[redacted]
LPC	lysophosphatidylcholine

mAb	monoclonal antibody
MMRM	Mixed Model for Repeated Measures
MOG-EAE	myelin oligodendrocyte glycoprotein-experimental autoimmune encephalomyelitis
[redacted]	[redacted]
MS	multiple sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
OLE	open-label extension
OPC	oligodendrocyte progenitor cell
PASAT-3	3-Second Paced Auditory Serial Addition Test
[redacted]	[redacted]
PK	pharmacokinetics
[redacted]	[redacted]
RMS	relapsing multiple sclerosis
[redacted]	[redacted]
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SD	standard deviation
[redacted]	[redacted]
SDMT	Symbol-Digit Modalities Test
SPMS	secondary progressive multiple sclerosis
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
[redacted]	[redacted]
T25FW	Timed 25-Foot Walk
T3	triiodothyronine
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone

3. SPONSOR INFORMATION

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

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

4. INTRODUCTION

LINGO-1 is a cell surface glycoprotein that is selectively expressed in the human central nervous system (CNS) but not in non-neural tissues [Barrette 2007; Carim-Todd 2003; Llorens 2008; Mi 2004; Okafuji and Tanaka 2005; Park and Hong 2006; Shao 2005]. It is a member of a newly discovered protein family comprising 3 other paralogs: LINGO-2 (GI: 12309630, 61% protein identity), LINGO-3 (GI: 23342615, 56% identity), and LINGO-4 (GI: 21211752, 44% identity). LINGO-1 is highly conserved evolutionarily with human and mouse orthologues sharing 99.5% identity.

LINGO-1 is selectively expressed in both oligodendrocyte progenitor cells (OPCs) and neurons, where it functions as a negative regulator of OPC differentiation and myelination [Lee 2007; Mi 2007; Mi 2005]. Its expression is developmentally regulated and is upregulated in CNS diseases and injury [Ji 2006; Mi 2004; Mi 2013]. Specifically, LINGO-1 expression is increased in OPCs from demyelinated white matter of multiple sclerosis (MS) brain tissues. LINGO-1 negatively regulates oligodendrocyte differentiation and myelination, neuronal survival, and axonal regeneration by activating ras homolog gene family member A and inhibiting Protein kinase B phosphorylation signaling pathways [Lee 2007; Mi 2005; Mi 2009; Mi 2013].

BIIB033 is a first-in-class human monoclonal antibody (mAb) directed against LINGO-1. BIIB033 enhances differentiation of primary rat, monkey, and human oligodendrocytes in vitro and enhances axonal myelination in an in vitro rat dorsal root ganglion/OPC co-culture bioassay. Additionally, BIIB033 enhances remyelination and functional recovery in the rat lysophosphatidylcholine (LPC), cuprizone, myelin oligodendrocyte glycoprotein-experimental autoimmune encephalomyelitis (MOG-EAE), and MOG-EAE optic neuritis models [Gresle 2016; Mi 2009].

The therapeutic hypothesis is that BIIB033 will act in the CNS to block LINGO-1. In turn, the inhibition of LINGO-1 may promote remyelination via differentiation of OPCs normally present in the CNS and to promote axonal regeneration. Therefore, BIIB033 treatment in demyelinating diseases such as MS may lead to improved CNS repair with corresponding beneficial effects on neurological function and disability.

4.1. Overview of Multiple Sclerosis

MS is a chronic autoimmune and neurodegenerative disorder of the CNS that is characterized by inflammation, demyelination, and oligodendrocyte and neuronal loss. It is the most common demyelinating disorder of the CNS, affecting approximately 2.5 million people worldwide. Its prevalence is highest among Caucasians, with higher rates reported in North America, Europe, Australia, New Zealand, and northern Asia [Noseworthy 2000; Rosati 2001].

Relapsing MS (RMS) is the most common clinical presentation of the disease. The term “relapsing MS” applies to patients with either relapsing-remitting MS (RRMS) or secondary progressive multiple sclerosis (SPMS) who experience relapses, which are considered part of the same disease spectrum. In the relapsing/remitting phase of the disease, patients experience episodes of neurological dysfunction (relapses) separated by periods of relative stability.

Relapses may completely subside in the early stage of the disease, but recovery tends to be incomplete over time, leading to the accumulation of physical disability and cognitive decline. RRMS is usually diagnosed between the ages of 20 and 40 years and affects twice as many women as men. As patients progress from RRMS to SPMS, they are more likely to experience progressive neurological decline with or without superimposed relapse. The median time to progression from RRMS to SPMS is approximately 10 years [Runmarker and Andersen 1993]. Approximately half of all MS patients are unable to walk without assistance within 15 years of their initial diagnosis [Runmarker and Andersen 1993; Weinshenker 1989], and more than half of patients die from MS or its complications [Brønnum-Hansen 2004].

Although CNS repair takes place early during the disease, the ability to repair the CNS eventually fails, leading to irreversible tissue injury and accumulation of disability. One leading hypothesis is that the failure of remyelination in MS is due in large part to inhibition of oligodendrocyte differentiation by LINGO-1. It is also hypothesized that the failure of axonal repair/neurite regeneration in MS is due to signaling of myelin debris on the Nogo66 receptor 1 (NgR1)/p75/LINGO-1 and NgR1/TROY/LINGO-1 complex in damaged axons [Ji 2006; Mi 2004]. Signaling on the NgR1 receptor complex may interfere not only with axonal regeneration [Yamashita 2005] but also with neuronal survival following neuroaxonal injury [Bourikas 2010; Fu 2008; Zhao 2008].

4.2. Current Therapies for Multiple Sclerosis

The current standard of care in RMS employs 2 general approaches: immunomodulatory drugs aimed at reducing the frequency and severity of relapses as well as the accumulation of physical disability, which includes interferon beta (IFNβ) products (Avonex®, Plegridy®, Betaferon®/Betaseron®/Extavia®, and Rebif®), glatiramer acetate (GA; Copaxone®), fingolimod (Gilenya®), teriflunomide (Aubagio®), dimethyl fumarate (DMF; Tecfidera®), natalizumab (Tysabri®), alemtuzumab (Lemtrada®), daclizumab (Zinbryta®), ocrelizumab (Ocrevus®), and mitoxantrone (Novantrone®), and drugs that provide symptomatic treatment as needed for depression, bladder dysfunction, and walking impairment.

There are currently no approved therapies to promote neurorepair in the CNS when the inflammatory aspects of the disease are controlled.

4.3. Profile of Previous Experience With BIIB033

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

4.3.1. Nonclinical Experience

BIIB033 is a fully human anti-LINGO-1 mAb that was engineered into an aglycosyl immunoglobulin G subclass 1 (IgG_1) framework to eliminate effector function. Histological and functional evaluations of LINGO-1 knock-out mice have been performed, and nonclinical studies have demonstrated the potential for LINGO-1 antagonism to enhance CNS remyelination and neuroaxonal protection in animal models of (1) toxic demyelination (Cuprizone) [Mi 2009],

(2) chemical demyelination (LPC), (3) inflammatory demyelination (MOG-EAE) [Mi 2007], (4) toxic neuronal injury (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [Inoue 2007] , and (5) traumatic/hypertensive optic nerve injury [Ji 2008; Ji 2006; Lv 2010].

The results of these studies indicate that BIIB033:

- Binds to LINGO-1 with similar high affinity across human, monkey, rat, and mouse.
- Is selective for LINGO-1 and does not bind the other LINGO family members, that is, LINGO-2, LINGO-3, or LINGO-4.
- Promotes differentiation of primary rat, monkey, and human oligodendrocytes in vitro.
- Promotes axonal myelination in an in vitro rat dorsal root ganglion/OPC co-culture bioassay.
- Has significantly reduced Fc (γ) and complement effector functions compared to wild-type IgG_1.
- Is efficacious in animal models using biochemical and functional readouts. Remyelination activity has been demonstrated in the rat LPC model following systemic administration from 1 to 100 mg/kg. Functional recovery in the rat MOG-EAE model has been demonstrated following weekly systemic administration of 3 and 10 mg/kg.
- Is efficacious in animal models when given in the presence of IFNβ or high-dose corticosteroids.

These results support the development of BIIB033 as a potential therapy for the treatment of MS.

4.3.2. Clinical Experience

Three Phase 1 studies and 2 Phase 2 studies have been completed. The Phase 1 studies included Studies 215HV101 (single-ascending dose study in healthy volunteers), 215MS101 (multiple-ascending dose study in subjects with RRMS or SPMS), and 215HV102 (single- and multiple-dose study in healthy Japanese volunteers). The Phase 2 studies included Study 215ON201 in subjects with acute optic neuritis (AON) and Study 215MS201 in subjects with relapsing form of MS.

In the Phase 1 studies, BIIB033 exposure was dose proportional over the studied dose levels and dose ranges, with doses ranging from 0.1 to 100 mg/kg. BIIB033 was well tolerated, and laboratory findings revealed no clinically meaningful abnormalities. BIIB033 pharmacokinetics (PK) in subjects with MS was similar to that observed in healthy adults, and BIIB033 PK does not appear to be altered by the concurrent treatment of IFNβ or GA. Additionally, the clinical study portions of an additional Phase 1 study have been completed. Study 215HV103 is a single-

dose study in healthy volunteers using study treatment from 2 different manufacturing processes (referred to as BIIB033-A and BIIB033-B). Preliminary data indicate that the PK parameters (area under the concentration-time curve from time 0 to infinity [AUC_{inf}] and maximum observed concentration [C_{max}]) are very similar for the BIIB033-A material and the BIIB033-B material.

The completed Phase 2 Study 215ON201 was a 24-week, randomized study designed to assess the efficacy, safety, tolerability, and PK of BIIB033 (100 mg/kg) versus placebo in 82 subjects with their first episode of AON.

- A trend in improvement was observed for the intent-to-treat (ITT) population in full-field visual evoked potential latency of the affected eye at both Weeks 24 and 32 with BIIB033 over placebo, compared with the baseline of the unaffected fellow eye. This improvement reached statistical significance in the per-protocol population at Week 32. These data provided proof-of-biology evidence for CNS remyelination with BIIB033 treatment.

- No treatment effects were observed in retinal thinning or visual acuity tests with BIIB033 over placebo.

- In this study, 100 mg/kg of BIIB033 infused IV every 4 weeks was well tolerated, and the overall incidence of adverse events (AEs) was the same in the placebo and BIIB033 groups (83%). Hypersensitivity reactions occurred in 2 subjects (5% of BIIB033-treated subjects who received 100-mg/kg dose), and postbaseline weight gain was also observed.

The completed Phase 2 Study 215MS201 was a 72-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study to assess the efficacy, safety, tolerability, and PK of BIIB033, when used concurrently with Avonex, in subjects with relapsing forms of MS. BIIB033 was evaluated at doses of 3, 10, 30, and 100 mg/kg.

- The primary endpoint was confirmed improvement in 1 or more assessments of a multicomponent disability endpoint over 72 weeks. A statistically significant linear dose-response on primary endpoint was not observed with BIIB033 treatment versus placebo (p=0.9831). Analyses showed a non-monotonic, inverted U-shaped dose response to BIIB033 with more favorable outcomes in the 10- and 30-mg/kg groups.

- Prespecified univariate subgroup analyses suggested enhanced efficacy in younger subjects and in those with clinical [redacted] features suggestive of more preserved brain tissue integrity. Analyses of individual functional assessments as well as the Overall Response Score also suggested a more pronounced favorable effect of BIIB033 at the 10-mg/kg dose, although there was a waning effect over time.

- Post hoc multivariate analysis showed a greater and more durable efficacy in a subpopulation (approximately 25% to 30% of the ITT population) defined by shorter

disease duration and baseline MRI characteristics consistent with lower myelin content but higher tissue integrity in T2 lesions, especially in the 10-mg/kg group.

- BIIB033 was generally well tolerated, with hypersensitivity reactions seen only at the 100-mg/kg dose (4 subjects [1% of BIIB033-treated subjects]) and a trend for dose-dependent weight gain over 72 weeks, with a mean increase between 0.9 and 1.9 kg in 4 BIIB033 dosing groups.

- The study showed no change in the PK profile of BIIB033 and no new safety signals.

The efficacy results observed in Study 215MS201, combined with the favorable safety profile demonstrated by the Phase 1 and Phase 2 studies as well as the proof of biology achieved in Study 215ON201, support the continued evaluation of BIIB033.

4.4. Study Rationale

4.4.1. Rationale for Part 1

The proposed study (215MS202) will further investigate the efficacy and safety of BIIB033 as an add-on therapy in subjects with RMS who are on a stable dose of an anti-inflammatory disease-modifying therapy (DMT) and with baseline characteristics consistent with projected enhanced treatment effect of BIIB033 as identified in the post hoc analysis from Study 215MS201. To reduce variability and potential confounding factors from different background DMTs while allowing for the evaluation of the effect of BIIB033 across a range of background therapies, 3 specific groups of background DMTs will be included in this study and randomization to treatment (BIIB033 or placebo) will be stratified by DMT group. The DMTs are IFNβ (Avonex, Plegridy, Betaferon/Betaseron, or Rebif), DMF (Tecfidera), and natalizumab (Tysabri), representing different mechanisms of action, anti-inflammatory activities, and routes of administration.

4.4.2. Rationale for Part 2: Open-Label Extension

The optional open-label extension study (Part 2) will investigate long-term safety and efficacy of BIIB033 treatment as an add-on therapy to anti-inflammatory DMTs for approximately 2 years (96 weeks) [redacted]. Part 2 will provide the opportunity to follow the safety and efficacy of BIIB033 treatment for approximately 3.5 years in participants who received BIIB033 in Part 1, [redacted]

4.5. Rationale for Dose and Schedule Selection

4.5.1. Part 1

Subjects will be randomized in a 1:1 ratio to receive either BIIB033 750 mg or placebo once every 4 weeks via IV infusion.

A total of 19 doses of study treatment will be administered.

Results from Phase 1 and Phase 2 studies suggest that IV doses of BIIB033 up to 100 mg/kg in healthy volunteers and MS patients were well tolerated. A total of 7 cases of hypersensitivity reactions all occurred in the 100-mg/kg dose group, led to discontinuation of treatment, and had an outcome of resolved. [redacted]

As described in the study rationale, Study 215MS201, a Phase 2 study evaluating BIIB033 doses ranging from 3 to 100 mg/kg in RRMS and SPMS subjects over 72 weeks demonstrated a nonmonotonic, inverted U-shaped dose response and a waning of effect over time. Positive signals were most consistently seen for the 10-mg/kg dose across a number of different analyses. In addition, the 10-mg/kg dose group also showed most pronounced efficacy in the subpopulation with larger and more durable efficacy in the post hoc multivariate analysis.

BIIB033 exhibits typical PK characteristics of IgG_1 mAb with an elimination half-life ($t_{1/2}$) of approximately 2 to 3 weeks, supporting once every 4 weeks IV infusion regimens in the Phase 2 studies. The 10-mg/kg dose regimen used in Study 215MS201 yielded mean average serum concentrations approximately 1.2-fold higher than the rat serum concentration at 90% of E_{max} (EC_{90}; adjusted for ~0.1% brain penetration). A population PK simulation analysis showed that a 750 mg fixed dose provides comparable exposure (C_{max}, minimum observed concentration [C_{min}], area under the concentration-time curve [AUC]) to the 10-mg/kg dose. In addition, exposure of 750 mg dosing has negligible overlap with 3 or 30 mg/kg dosing. Therefore, BIIB033 750 mg infused IV every 4 weeks will be the dose regimen for the current proposed study.

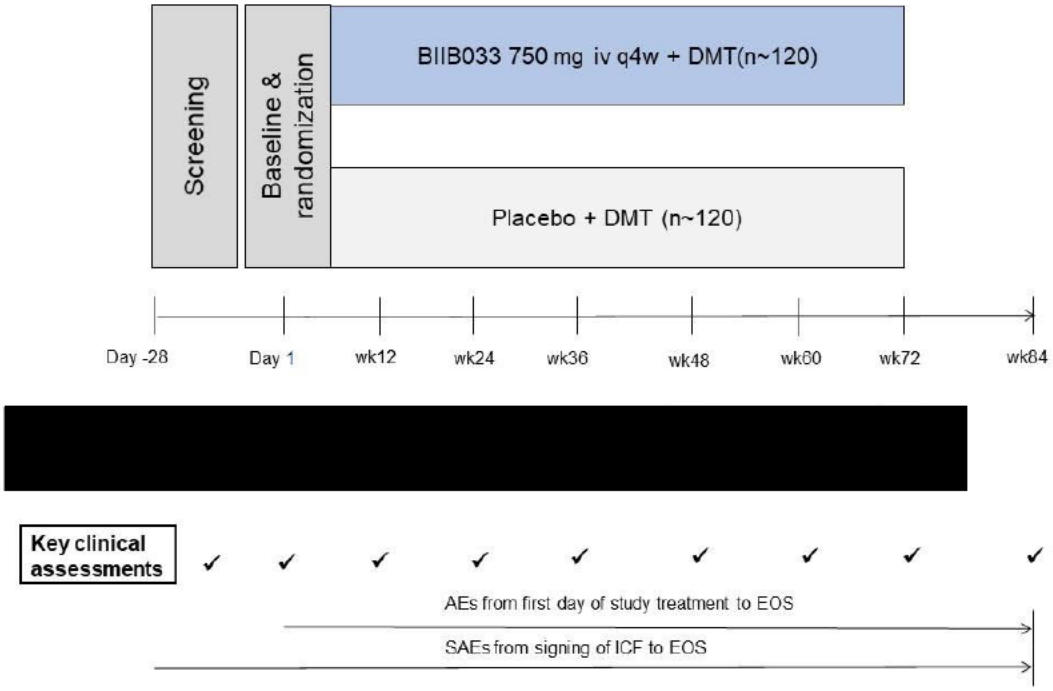
4.5.2. Part 2

The rationale for BIIB033 dose and schedule selection is the same as that in Part 1. Subjects participating in Part 2 will not receive placebo.

5. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES

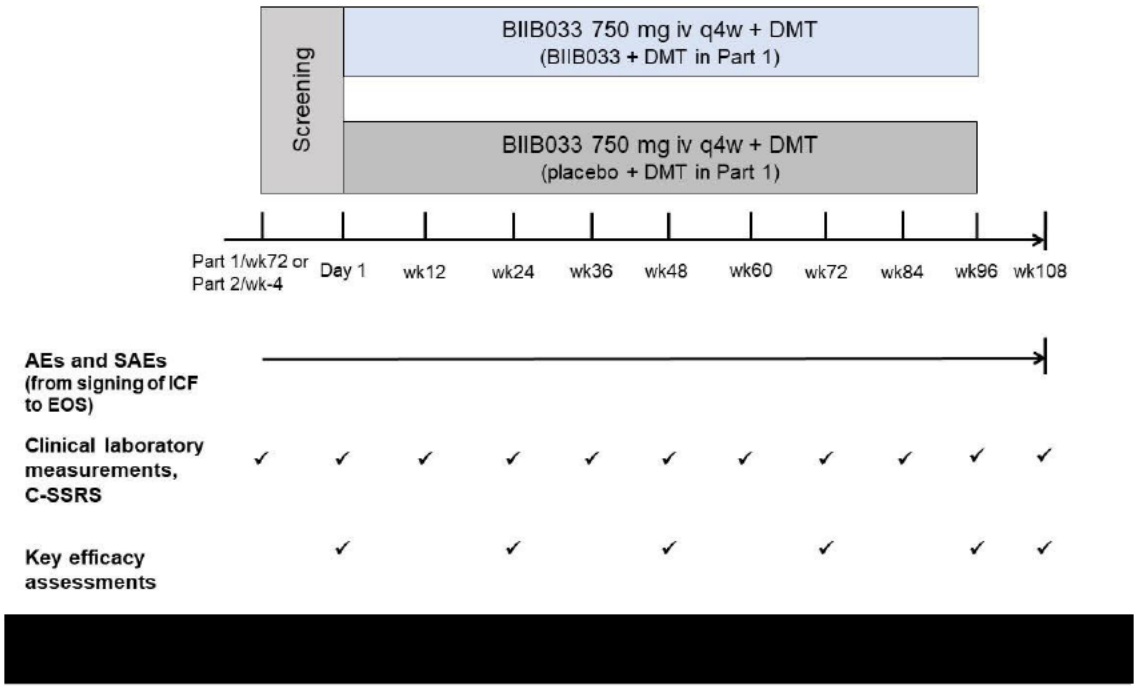
5.1. Study Schematics

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

5.2. Part 1 – Schedule of Activities

Table 1: 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	
Urinalysis	X	X[2]	X	X	X	X	X	X			X			X	
Serum FSH[9]	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**
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; Gd=gadolinium; 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 2 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]

[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 2: 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
[redacted]								

	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**
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 Table 3).

[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, [redacted], 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.

5.3. Part 2 – Schedule of Activities

Table 3: 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

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**
[redacted]															
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[17]		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; Gd=gadolinium; 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] Tests and assessments 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.

[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, [redacted], 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]

[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.

[redacted]

Table 4: 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
T25FW, 9HPT-D, 9HPT-ND[6]					X						X	X[6]	X	X
SDMT					X						X	X[6]	X	X
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
Blood chemistry		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**
Urinalysis		X			X			X			X	X[9]	X	X
Urine pregnancy test[10]	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**
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, [redacted], 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]

[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]

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Part 1 Objectives and Endpoints

Table 5: Part 1 Objectives and Endpoints

Primary Objective	**Primary Endpoint**[1]
To evaluate the effects of BIIB033 versus placebo on disability improvement over 72 weeks.	The primary endpoint is the Overall Response Score, assessed over 72 weeks of the study. The Overall Response Score 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 Overall Response Score that ranges from +4 to -4 for each visit.
Secondary Objective	**Secondary Endpoints**[1]
To evaluate the effects of BIIB033 versus placebo on additional measures of disability improvement	• Proportion of subjects with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND • Proportion of subjects with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, or PASAT-3 • Proportion of subjects with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or

	9HPT-ND, and without confirmed worsening in any of the 4 assessments during the 72 weeks of the study • Proportion of subjects with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 9HPT-ND, and SDMT • Proportion of subjects with 12-week confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND (20% thresholds for T25FW and 9HPT)
Tertiary Objectives	**Tertiary Endpoints[1]**
[redacted]	[redacted]

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

9HPT-D=9-Hole Peg Test, dominant hand; 9HPT-ND=9-Hole Peg Test, nondominant hand; AE=adverse events; C-SSRS=Columbia Suicide Severity Rating Scale; [redacted]; ECG=electrocardiogram; EDSS=Expanded Disability Status Scale; EMS=Early Multiple Sclerosis; [redacted]; MS=multiple sclerosis; [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

[1] For T25FW, 9HPT-D, 9HPT-ND, and PASAT-3, 15% thresholds (i.e., ≥15% change from baseline) are used to measure improvement or worsening unless otherwise specified. For EDSS, improvement is defined as a ≥1.0-point decrease in EDSS from a baseline score of ≤6.0, and worsening is defined as a ≥1-point increase from a baseline score of ≤5.5 or a ≥0.5-point increase from a baseline score equal to 6.0. For SDMT, improvement is defined as a ≥4-point increase from baseline, and worsening is defined as a ≥4-point decrease from baseline.

6.2. Part 2 Objectives and Endpoints

The BIIB033 Treatment Baseline in Part 2 is defined as the timepoint when the first dose of BIIB033 was given, i.e., Part 1/Day 1 for subjects treated with BIIB033 in Part 1, and as Part 2/Day 1 for subjects treated with placebo in Part 1.

Table 6: Part 2 Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate the long-term safety profile of BIIB033 as an add-on therapy in subjects with MS	• Incidence of AEs and SAEs over 96 weeks in Part 2
Secondary Objective	**Secondary Endpoints**
To investigate long-term efficacy (disability improvement) and additional safety measures of BIIB033 as an add-on therapy in subjects with MS	• Overall Response Score over 96 weeks in Part 2 • Proportion of subjects with 24-week confirmed improvement 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 confirmed improvement 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 confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, or 9HPT-ND, and without confirmed worsening in any of the 4 assessments during the 96 weeks of the study • Proportion of subjects with 24-week confirmed improvement 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 confirmed improvement in at least 1 of the following assessments: EDSS, T25FW, 9HPT-D, 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 • C-SSRS score over 96 weeks in Part 2
Tertiary Objectives	**Tertiary Endpoints**
[redacted]	[redacted]

; 9HPT=9-Hole Peg Test; 9HPT-D=9-Hole Peg Test, dominant hand; 9HPT-ND=9-Hole Peg Test, nondominant hand; ADL=Activities of Daily Living; AE=adverse events; C-SSRS=Columbia Suicide Severity Rating Scale; ;

ECG=electrocardiogram; EDSS=Expanded Disability Status Scale; EMS=Early Multiple Sclerosis; FT4=free thyroxine; [redacted]; MS=multiple sclerosis; [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; T3=triiodothyronine; TSH=thyroid-stimulating hormone

7. STUDY DESIGN

7.1. Study Overview

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 (as defined in Section 4.4) and will continue taking their DMT throughout the study.

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

- Screening (pretreatment)
- Treatment Period: 1 visit every 4 weeks between Baseline/Day 1 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.

7.2. 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 who enroll in Part 2 do not need to have the 12-week postdose follow-up (EOS); 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.

7.2.1. Screening

For Part 1, subject eligibility for the study will be determined at Screening within 28 days prior to Day 1/Baseline.

For subjects participating in Part 2, Part 1/Week 72 will be the combined Part 1 Final Visit and the Part 2 Screening Visit. In case the Part 2 Screening Visit is unable to be performed at Part 1/Week 72, a separate visit may occur within 4 weeks prior to Part 2/Day 1 (see Section 5.3).

7.2.2. Treatment Period

Part 1

Study treatment with BIIB033 or placebo will be initiated on Day 1 after all baseline assessments are completed.

The Treatment Period will consist of 19 study visits beginning with Day 1/Baseline and then every 4 weeks at Weeks 4 through Week 72 with a visit window of ±5 days (see Section 5).

Subjects who do not enroll in Part 2 will return to the study site for a post-treatment EOS Visit at Week 84, 12 weeks±10 days after the last dose of BIIB033 or placebo.

Part 2

Study treatment with BIIB033 will be initiated on Day 1 after all Part 2/Day 1 assessments are completed.

The Treatment Period will consist of 25 study visits beginning with Day 1 and then every 4 weeks at Weeks 4 through Week 96 with a visit window of ±5 days (see Table 3 and Table 4).

7.2.3. Unscheduled Visit(s) and Treatment for Relapse

If an MS relapse is suspected during the study, the subject should return to the study site for an unscheduled visit and be evaluated as soon as possible (within 5 days after onset of the event) for confirmation and to determine the severity of the relapse. Relapses will be documented in the relapse assessment form.

An MS relapse will be defined as the onset of new or recurrent neurological symptoms lasting at least 24 hours, accompanied by new objective abnormalities on a neurological exam, and not explained solely by non-MS processes such as fever, infection, severe stress, or drug toxicity (adapted from [Schumacher 1965]).

The subject must have objective signs confirming the event on the *examining neurologist's* examination.

New or recurrent neurological symptoms that occur less than 30 days following the onset of a protocol-defined relapse should be considered as part of the same relapse. New or recurrent neurologic symptoms that evolve gradually over months should not be considered an acute relapse and should not be treated with high-dose corticosteroids. Laboratory tests to investigate possible causes of pseudorelapse can be done at the discretion of the Investigator.

Treatment of a protocol-defined relapse may proceed at the discretion of the Investigator according to local standards of care and will not affect the subject's eligibility to continue in the study. At the discretion of the Investigator, treatment may include 1000 mg IV methylprednisolone administered daily for 3 to 5 days with or without an oral prednisone taper (up to 15 days).

[redacted]

7.2.4. Follow-Up

Part 1

Subjects who enroll in Part 1 but not Part 2 will return to the study site for an End of Part 1 Evaluation approximately 12 weeks after the last dose of study treatment (Part 1/Week 72 Visit). Subjects who enroll in Part 2 do not need to have the Part 1 12-week postdose follow-up (EOS) Visit.

Part 2

Subjects will return to the study site for a post-treatment EOS Visit at Week 108, 12 weeks±10 days after the last dose of BIIB033.

7.3. Responsibilities of Study Site Personnel

For each subject in Part 1 and Part 2, the Principal Investigator of the site will designate the following investigational site personnel:

- A primary and backup *treating neurologist*
- A *treating nurse* (or study coordinator; may be performed by treating neurologist)
- A primary and backup *examining neurologist*
- An *examining technician* (may be performed by examining neurologist)
- [redacted]
- An unblinded *pharmacist* (or unblinded authorized designee)

Both the *examining neurologist* and the *treating neurologist* must have a minimum of 2 years of neurology specialty training and, at study initiation, do not anticipate to leave the study within at least 1 year. Where specified, evaluations described in this section must be performed only by the personnel indicated. Treating neurologists may review neurological exam results obtained by examining neurologists. The *examining neurologist* and *examining technician* should not administer study treatment.

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

- Management of the routine neurological care of the subject, including the management of background DMT treatment and associated safety monitoring
- Assessment (including assignment of causality) and treatment of AEs and MS relapses
- Review of hematology and blood chemistry results from the central laboratory to assess whether the subject's study treatment should be discontinued as per the criteria detailed in Section 10
- The *treating neurologist* may designate the backup *treating neurologist* or the *treating nurse* at the investigational site to perform some of the tests and evaluations listed under "*treating neurologist*." If there is more than 1 *treating neurologist* available at a given site such that each one is assigned to particular subjects, then these *treating neurologists* may act as backup for each other.

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

The primary *treating nurse* (or study coordinator; may be performed by *treating neurologist*) will be responsible for the following:

- Assisting the treating neurologist in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medications
- [redacted]
- Administering the Columbia Suicide Severity Rating Scale (C-SSRS)
- Collecting blood samples and obtaining vital signs

The *examining neurologist* will be responsible for the following:

- Obtaining an Expanded Disability Status Scale (EDSS) score based on a detailed neurological examination at the scheduled timepoints required in the protocol
- Obtaining an EDSS score at every Unscheduled Relapse Assessment Visit if referred by the *treating neurologist* when there is the possibility of a relapse
- The following guidelines must be strictly followed:
  - The *examining neurologist* must not be involved with any other aspect of subject care and management. Further, the *examining neurologist* is not to serve as *treating neurologist* for any subjects at a given investigational site.
  - The *examining neurologist* must remain blinded to AEs, concomitant medications, laboratory data, [redacted], and any other data that have the potential of revealing the treatment assignment.
  - To ensure consistency across sites, *examining neurologists* and the backup *examining neurologist* must receive standardized training and obtain certification of EDSS scoring prior to enrollment of subjects at their site.
  - The backup *examining neurologist* will conduct subject evaluations ONLY if the primary *examining neurologist* is unavailable due to illness, vacation, or travel.

All sites should attempt to maintain the same *examining neurologist* throughout the study.

- If an *examining neurologist* has to be replaced, the new *examining neurologist* must receive standardized training and obtain certification of EDSS scoring prior to performing an EDSS assessment.

- The communication of new findings on the neurological examination from the *examining neurologist* to the *treating neurologist* is permitted (because findings on the neurological examination may be important in the routine care of the subject, e.g., medical management of relapses).

- The roles of the *treating* and *examining neurologists* (primary and backup) are NOT interchangeable even for different subjects.

- The *examining neurologist* may also act as the *examining technician* (see below).

- After receiving approval from the Biogen Medical Director or designee, nurse practitioners or physician assistants who have at least 2 years of practice experience in a neurology clinic and have prior experience and certification in EDSS scoring may function as examining neurologists in this study.

The *examining technician* (or the examining neurologist) will be responsible for the following:

- Administering the Timed 25-Foot Walk (T25FW), 9HPT-D, 9HPT-ND, 3-Second Paced Auditory Serial Addition Test (PASAT-3), Symbol-Digit Modalities Test (SDMT), [redacted], [redacted] at each scheduled timepoint required in the protocol

- These guidelines must be strictly followed:

  - The *examining technician* must remain blinded to AEs, concomitant medications, laboratory data, [redacted], and any other data that have the potential of revealing the treatment assignment.

  - To ensure consistency across sites, *examining technicians* must undergo a standardized training session prior to enrollment of subjects at their site.

  - All sites should attempt to maintain the same *examining technician* throughout the study.

  - If an *examining technician* has to be replaced, the new *examining technician* must undergo a training session prior to performing any study assessment.

[redacted]

The unblinded *pharmacist* (or unblinded authorized designee) will be responsible for the following:

- Receipt, storage, distribution, and accountability of study treatment
- Storage and security of unblinding documentation related to study treatment, dose preparation, and study treatment assignment. All treatment assignment or study treatment preparation information must be maintained strictly confidential at all times. Measures to prevent inadvertent unblinding must be followed.
- Preparation of study treatments for IV infusion

7.4. Study Stopping Rules

For Part 1 and Part 2 of the study, Biogen may terminate this study at any time, after informing Investigators. Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

7.5. End of Study

The End of Study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria – Part 1

To be eligible to participate in this study, subjects must meet the following eligibility criteria at Screening or at the timepoint specified in the individual eligibility criterion listed:

1. Ability of the subject to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.

2. Age 18 to 58 years old, inclusive, at the time of informed consent.

3. Diagnosis of RRMS per the 2010 McDonald's criteria [Polman 2011] or onset of SPMS per the Lublin and Reingold criteria [Lublin 2014].

4. Baseline EDSS score of 2.0 to 6.0.

5. MS disease duration of ≤20 years from first MS symptom(s).

6. Must have at least one of the following occurring within 24 months prior to Day 1/Baseline:

   - Clinical relapse(s) [but not within 24 weeks prior to Day 1/Baseline]
   - Gadolinium (Gd)-enhancing lesion(s) on brain or spinal cord MRI
   - New T2 lesion(s) on brain or spinal cord MRI

7. Must have been taking one of the following DMTs at a stable dose for at least 24 weeks prior to Day 1/Baseline:

   - IFNβ (Avonex, Plegridy, Betaferon/Betaseron, or Rebif [at 44 µg by subcutaneous injection 3 times per week])
   - DMF (Tecfidera)

- Natalizumab (Tysabri)
  Subjects who missed no more than a single dose of natalizumab during the 24-week period may still enter the study.

8. At enrollment, subject is not anticipated to require switching of background anti-inflammatory DMT, in the opinion of the Investigator.

9. All subjects must meet the following MRI criteria on the Screening/Baseline brain MRI:

   - MTR in T2 lesions ≤-0.17 normalized MTR unit (nMTRu)

   and

   - DTI – radial diffusivity (DTI-RD) in T2 lesions $\leq 0.98 \times 10^{-3}$ mm^2/s

10. All female subjects of childbearing potential and all male subjects must practice effective contraception during the study and continue contraception for at least 24 weeks after their last dose of study treatment (BIIB033 or placebo). In addition, subjects should not donate sperm or eggs during the study and for at least 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, refer to Section 15.5.

8.2. Exclusion Criteria – Part 1

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening or at the timepoint specified in the individual criterion listed:

1. Primary progressive MS [Polman 2011].

2. T25FW >30 seconds (based on an average of 2 consecutive trials at Screening).

3. An MS relapse that has occurred within 24 weeks prior to Day 1/Baseline or the subject has not stabilized from a previous relapse at the time of Screening.

4. A history of clinically significant persistent neutralizing antibody against IFNβ or natalizumab, in the opinion of the Investigator, for subjects treated with an interferon or with natalizumab, respectively.

5. Prior exposure to BIIB033 (opicinumab).

6. Treatment with any chemotherapeutic agents (e.g., mitoxantrone, cyclophosphamide, cladribine), cell-depleting mAbs (e.g., rituximab, ocrelizumab, alemtuzumab), total lymphoid irradiation, T-cell or T-cell receptor vaccination, or teriflunomide within 1 year prior to Day 1/Baseline.

7. Treatment with other anti-inflammatory DMTs (e.g., GA, fingolimod, daclizumab) or plasmapheresis within 24 weeks prior to Day1/Baseline.

8. Treatment with Botox for limb spasticity within 24 weeks before Day 1/Baseline.

9. Treatment with any investigational drug within 24 weeks or 5 $t_{1/2}$ (whichever is longer) prior to Day 1/Baseline.

10. Treatment with 4-aminopyridine (4-AP) within 30 days prior to Day 1/Baseline, unless a stable dose has been maintained for at least 30 days prior to Day 1/Baseline and will be continued for the course of this study. Treatment with medical marijuana for MS symptoms is not exclusionary, if it is consistent with local MS treatment guidelines and local regulations.

11. Treatment with high-dose oral or IV steroids within 30 days before Day 1/Baseline.

12. Contraindications to MRI, for example, presence of pacemakers or other implanted metal devices (excluding dental braces), an allergy to Gd, renal impairment, or claustrophobia that cannot be medically managed.

13. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered within 5 half-lives of the agent prior to the Baseline Visit. Participation in a noninterventional study can be allowed as long as this participation does not interfere with this protocol or is not likely to affect the subject's ability to comply with the protocol.

14. History of suicidal ideation or an episode of clinically severe depression (as determined by the Investigator) within 12 weeks of enrollment. Note: Subjects receiving ongoing antidepressant therapy will not be excluded from the study unless the medication has been increased within 24 weeks prior to enrollment.

15. History of human immunodeficiency virus or other immunodeficient conditions.

16. Positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for hepatitis B surface antigen or hepatitis B core antibody).

17. History of malignancy; however, subjects with a history of excised or treated basal cell carcinoma or fewer than 3 squamous cell carcinomas are eligible to participate in this study.

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

19. History of abnormal laboratory results that, in the opinion of the Investigator, are indicative of a significant cardiac, endocrine, hematologic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurologic (other than MS), and/or other major diseases.

20. Any of the following abnormal blood tests at Screening:

    - hemoglobin ≤9.0 g/dL
    - platelets $\leq 100 \times 10^9$/L
    - lymphocytes $\leq 1.0 \times 10^9$/L
    - neutrophils $\leq 1.5 \times 10^9$/L
    - alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), or gamma-glutamyl-transferase ≥2 times the upper limit of normal
    - creatinine clearance <60 mL/min (estimated by Cockcroft-Gault equation)

21. Female subjects who have a positive pregnancy test result, are pregnant, or are currently breast feeding.

22. Plans to undergo elective major procedures/surgeries at any time during the study.

23. Inability to comply with study requirements.

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

8.3. Inclusion Criteria – Part 2

1. Ability of the subject to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.

2. Subjects who complete study treatment (BIIB033 or placebo) at Part 1/Week 72 Visit.

3. All female subjects of childbearing potential and all male subjects must practice effective contraception during the study and continue contraception for at least 24 weeks after their last dose of BIIB033. In addition, subjects should not donate sperm or eggs during the study and for at least 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, refer to Section 15.5.

8.4. Exclusion Criteria – Part 2

Candidates will be excluded from the Part 2 if they meet any of the following exclusion criterion at the Part 2 screening:

1. Subjects who did not complete study treatment in Part 1/Week 72 Visit

2. Subjects who have a duration >12 weeks between their Part 1/Week 72 Visit and Part 2/Day 1.

3. Any significant change in clinical status that would make the subject unsuitable to participate in Part 2, in the opinion of the Investigator. The Investigator must reassess the subject's medical fitness for participation and consider any diseases that would preclude study treatment.

4. A history of clinically significant and persistent neutralizing antibody against IFNβ or natalizumab, in the opinion of the Investigator, for subjects treated with an interferon or with natalizumab, respectively.

5. Treatment with any investigational drug within 12 weeks prior to Part 2/Day 1.

6. Treatment with 4-aminopyridine (4-AP) within 30 days prior to Part 2/Day 1, unless a stable dose has been maintained for at least 30 days prior to Part 2/Day 1. Treatment with medical marijuana for MS symptoms is not exclusionary, if it is consistent with local MS treatment guidelines and local regulations.

7. Treatment with high-dose oral or IV steroids within 30 days before Part 2/Day 1.

8. Contraindications to MRI, for example, presence of pacemakers or other implanted metal devices (excluding dental braces), an allergy to Gd, renal impairment, or claustrophobia that cannot be medically managed.

9. Current enrollment or a plan to enroll in any interventional clinical study (except 215MS202) in which an investigational treatment or approved therapy for investigational use is administered within 12 weeks prior to the Part 2/Day 1. Participation in a noninterventional study can be allowed as long as this participation does not interfere with this protocol or is not likely to affect the subject's ability to comply with the protocol.

10. History of suicidal ideation or an episode of clinically severe depression (as determined by the Investigator) within 12 weeks prior to Part 2/Day 1.

11. History of human immunodeficiency virus or other immunodeficient conditions not related to DMT treatment.

12. History of malignancy unless enrollment is approved by the Sponsor; subjects with a history of excised or treated basal cell carcinoma or fewer than 3 squamous cell carcinomas are eligible to participate in this study.

13. History of drug or alcohol abuse (as defined by the Investigator) during Part 1 of the study or within 12 weeks prior to Part 2/Day 1.

14. History of abnormal laboratory results that, in the opinion of the Investigator, are indicative of a significant cardiac, endocrine, hematologic, immunologic, metabolic,

urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurologic (other than MS), and/or other major diseases.

15. Any of the following abnormal blood tests at Part 2 Screening:

    - alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), or gamma-glutamyl-transferase ≥2 times the upper limit of normal

    - creatinine clearance <60 mL/min (estimated by Cockcroft-Gault equation)

16. Female subjects who have a positive pregnancy test result, are pregnant, or are currently breast feeding.

17. Plans to undergo elective major procedures/surgeries at any time during the study.

18. Inability to comply with study requirements.

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

9. SCREENING AND RANDOMIZATION

9.1. Screening and Enrollment

Part 1

Subjects must provide informed consent before any Screening tests are performed (see Section 17.3). At the time of consent, the subject will be enrolled into the study. Subjects who are not eligible for participation at Screening due to a nonclinically significant out-of-range laboratory result(s) or a temporary condition (e.g., acute infection) may be rescreened 1 time only, at the discretion of the Investigator.

Participating study sites are required to document all screened candidates initially considered for inclusion in the study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the Screening log. A minimal set of Screening failure information is required to ensure transparent reporting of Screening failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, Screening failure details, eligibility criteria, and any serious adverse events (SAEs).

It is not required that all Screening tests and assessments be completed during 1 pretreatment visit. Subjects must 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 from each.

[redacted]

Part 2

Subjects must provide informed consent before any Part 2 assessments are performed (see Section 5.3). [redacted]

For subjects participating in Part 2, Part 1/Week 72 will be the combined Part 1 Final Visit and the Part 2 Screening Visit. In case the Part 2 Screening Visit is unable to be performed at Part 1/Week 72, a separate visit may occur within 4 weeks prior to Part 2/Day 1. The Part 2/Day 1 Visit should be performed as early as possible within 4 to 12 weeks from the Part 1/Week 72 Visit. Part 2/Day 1 must be within 12 weeks from Part 1/Week 72.

Subjects who are not eligible for participation at Screening due to a nonclinically significant out-of-range laboratory result(s) or a temporary condition (e.g., acute infection), or treatment with high dose steroids for a relapse, may be rescreened 1 time only, at the discretion of the Investigator.

The tests and assessments completed at the Part 1 Week 72 Visit may be used as Part 2 screening, and do not need to be repeated, if the subject enrolls in Part 2 within 4 weeks (+ 5 days) of the Part 1 Week 72 Visit.

Participating study sites are required to document all screened candidates initially considered for inclusion in the study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the Screening log. A minimal set of Screening failure information is required to ensure transparent reporting of Screening failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, Screening failure details, eligibility criteria, and any serious adverse events (SAEs).

9.2. Randomization

Part 1

Randomization will take place across all study sites using a centralized interactive response technology (IRT; see Section 19.1.2 for IRT vendor and training). Subjects will be randomized to receive BIIB033 or placebo in a 1:1 ratio.

Subjects will be randomized after all Screening assessments have been completed, including a stable pretreatment EDSS score, and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. Subjects will be assigned a unique 6-digit subject identification number (the first segment of the number represents the study site and the second segment of the number represents the subject at that study site) that will be used on study-related documents pertaining to the subject. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment or continue in the study.

Randomization will be stratified by MS type (RRMS versus SPMS), background DMT group, [redacted].

Subjects will be randomized via IRT. Each background DMT group should be represented by at least 10%, but no more than 45%, of the study population at enrollment. [redacted]

Subjects with RMS (RRMS and relapsing SPMS) will be enrolled in the study. It is estimated that 15% of enrolled subjects or fewer will have a diagnosis of relapsing SPMS.

Part 2

There will be no randomization in Part 2, the OLE phase of the study in which all subjects receive BIIB033.

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

9.3. Blinding Procedures

Part 1

All study staff will be blinded to the subject treatment assignments (BIIB033 or placebo), with the exception of the unblinded pharmacist or unblinded designee, who is responsible for preparing study treatments, and the unblinded Pharmacy Monitor. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or at Biogen, except the unblinded Pharmacist or designee and the unblinded Pharmacy Monitor. In addition, the Sponsor staff conducting the study along with the study Data Manager and study Statistician will also be blinded to the treatment allocations while the study is ongoing. Unblinded documentation will be clearly marked as containing unblinding information. Unblinded documentation will be stored in a secure location that will be inaccessible to blinded staff.

See Section 15.4.3.1 for instructions on unblinding in the event of a medical emergency.

All efficacy assessments and neurological examinations will be performed by an *examining neurologist* and/or *examining technician* blinded to treatment assignment. It is imperative that subject treatment assignments and any information (such as laboratory results, AE reports, clinical records, etc.) that may reveal the identity of the assigned treatment are not shared with the *examining neurologist* or *examining technician*.

The *examining neurologist*, *examining technician,* and subjects will be instructed to keep conversation to a minimum during evaluations and, in particular, not to discuss the potential side effects of study treatment. Similarly, there should be no access to patient records or prior assessments.

[redacted]

Part 2

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

At the end of Part 2 (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, Biogen will provide the randomization codes to Investigators, who then can inform their subjects about the treatment received. Unblinded documents from Part 1 will not be accessible to subjects or blinded site study staff before Part 2 ends.

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

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment (BIIB033 or placebo) for any of the following reasons:

- The subject withdraws consent.
- The subject becomes pregnant. Study treatment must be discontinued immediately.
- The subject experiences a medical emergency that necessitates permanent discontinuation and/or unblinding of study treatment.
- At the discretion of the Investigator for medical reasons or for noncompliance.

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

In Part 1 of the study, subjects who discontinue study treatment may remain in the study and continue protocol-required tests and assessments.

In Part 2, subjects who discontinue study treatment will be required to withdraw from the study.

10.2. Lost to Follow-Up

Subjects will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, that subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10.3. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject is unwilling or unable to comply with the protocol.
- The subject discontinues study treatment in Part 2.

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

In Part 1 and Part 2, subjects who withdraw from the study prematurely should complete an ET visit as soon as possible but no later than 4 weeks after the last dose of study treatment and an EOS Visit 12 weeks (±10 days) after the last dose of BIIB033 or placebo administration.

Subjects who withdraw from Part 1 of the study may not be replaced unless the dropout rate is higher than the expected rate.

11. STUDY TREATMENT USE

Biogen will provide BIIB033 to the study sites.

Refer to Section 12 (Study Treatment Management) for specifics on the preparation, storage, handling, disposal, and accountability of the study treatment.

11.1. Regimen

11.1.1. BIIB033 and Placebo

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

Part 1

BIIB033 or placebo will be administered as an IV infusion once every 4 weeks for 72 weeks at the study site.

Subjects will receive BIIB033 or placebo at 19 study visits (Day 1/Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, and Week 72).

BIIB033 or placebo should be administered within the ±5-day window period of the scheduled visit. If a subject misses the planned dose (i.e., outside of the ±5-day window), the missed dose should be administered as soon as possible unless it is within 2 weeks of the next scheduled dose (i.e., do not administer the missed dose if it is ≤2 weeks to the next scheduled dose).

Part 2

In Part 2 of the study, each subject will receive BIIB033 as an IV infusion once every 4 weeks (within ±5 day window of the scheduled visit) for 96 weeks, as specified in Table 3 and Table 4.

11.2. Modification of Dose and/or Treatment Schedule

Not applicable.

11.3. BIIB033 Precautions

Following BIIB033 or placebo administration, subjects will be required to remain at the study site for at least 1 hour for monitoring of any unexpected infusion reactions. Medications for the treatment of severe hypersensitivity reactions (e.g., epinephrine for subcutaneous injections, diphenhydramine for injection) should be available for immediate use.

Please refer to the DHA for detailed instructions.

11.4. Treatment Compliance

All doses of study treatment will be administered by the clinical staff.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between signing of the Informed Consent Form (ICF) and the EOS/ET Visit (Part 1, Week 84 ± 10 days; Part 2, Week 108 ± 10 days). Prior MS treatment should be recorded in the eCRF at Screening and Day 1/Baseline for Part 1.

11.5.1.1. Allowed Concomitant Therapy

11.5.1.1.1. Background Anti-Inflammatory DMTs for Use with Study Treatment

During the study period, subjects will take the same protocol-specified anti-inflammatory DMT they have been treated with for at least 24 weeks prior to Day 1/Baseline of Part 1. In Part 2, the subject will continue the anti-inflammatory background DMT used at the end of Part 1.

DMTs are not provided by Biogen and are managed by the treating neurologist. Treating neurologists will be responsible for the prescription of background DMT treatment and safety monitoring according to the local label and regulations.

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. Subsequent infusions of natalizumab should be managed in accordance with its label. BIIB033 can be administered again on the same day if no infusion reaction occurs during subsequent natalizumab infusions.

Administration of background DMTs may continue after the study Treatment Period ends, at the discretion of the treating neurologist.

Based on the clinical judgment of the treating neurologist, subjects can switch to another marketed DMT during the study (not limited to protocol-defined DMTs) or may discontinue the DMT altogether. These subjects should remain in the study and continue study treatment (BIIB033 or placebo). The reason for the change and the DMT that the subject switched to (if applicable) must be recorded in the subject's eCRF. Investigators continue to be responsible for managing DMT treatment and safety monitoring after a switch.

The Medical Monitor should be notified of any DMT switches.

11.5.1.1.2. Other Allowed Concomitant Therapy

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

Concomitant therapy with the following is allowed as long as the exclusion criteria listed in Section 8.2 and Section 8.4 are observed:

- Oral contraceptives at a stable dose for women of childbearing potential.
- Acetaminophen/paracetamol for pain relief or treatment of flu-like symptoms.
- 4-AP, if used per label and maintained on a stable regimen for at least 30 days prior to Part 1/Baseline or Part 2/Day 1, and throughout the study.
- Medications used to treat MS symptoms, such as spasticity, bladder impairment, pain, or depression (such symptomatic therapy is not restricted, but should be optimized as early as possible during Screening in an attempt to maintain consistent treatment for the duration of the study). Medical marijuana is allowed for treatment of MS symptoms if it is consistent with local MS treatment guidelines and local regulations, is maintained on a stable regimen for at least 30 days prior to Part 2/Day 1, and throughout the study.
- Steroid treatment of a protocol-defined relapse at the discretion of the treating neurologist according to local standards of care (refer to Section 7.2.3).
- Corticosteroids that are administered by nonsystemic routes (e.g., topical, inhaled).

11.5.1.2. Disallowed Concomitant Therapy

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

- While subjects are permitted to switch from their protocol-defined background DMT to another marketed background DMT at the discretion of their treating neurologist, subjects are not allowed to take more than 1 background DMT at any time; this includes any chronic immunosuppressant or immunomodulatory therapy.
- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications
- Any systemic steroid therapy without prior approval from the Sponsor. This includes, but is not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., every 4 weeks) treatment with IV methylprednisolone, except for protocol-defined treatment of relapses (Section 7.2.3). Steroids that are administered by nonsystemic routes (e.g., topical, inhaled) are allowed.

Subjects who receive any of these restricted medications may be required to permanently discontinue study treatment and withdraw from the study (Sections 10.1 and 10.3). Contact Sponsor or designee for approval if specific medical conditions necessitate the use of any disallowed concomitant medications.

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

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is enrolled in the study (i.e., has signed the ICF) and the EOS/ET Visit unless the subject is being followed for study-related toxicity.

Total lymphoid irradiation, T-cell or T-cell receptor vaccination, plasmapheresis, or cytapheresis are not allowed during the study period.

Subjects who receive any of these restricted procedures may be required to permanently discontinue study treatment and may be withdrawn from the study as described in Sections 10.1 and 10.3.

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

11.6. Continuation of Treatment

Given that this is a Phase 2 study intended to provide proof of concept, no further provisions of the study treatment are made beyond the protocol-specified treatment duration.

12. STUDY TREATMENT MANAGEMENT

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice. Study treatment (BIIB033) will be stored in a limited-access area, out of sight and view to blinded site staff. Daily minimum/maximum temperature logs should be maintained at the study sites. Accountability for study treatment is the responsibility of the unblinded pharmacist (or unblinded authorized designee). More details concerning this responsibility are included in Section 12.1.4.

Study treatment must be dispensed only by an unblinded pharmacist (Part 1 only) or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatments are for one-time use only; do not use any study treatment remaining in the vial for another subject.

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

12.1. BIIB033

The BIIB033 used in this study will be BIIB033-B, whose production reflects process changes for improved efficiency and productivity relative to the BIIB033-A product used in previous clinical studies (see Section 4.3.2 [Study 215HV103] and the Investigator's Brochure for more details).

BIIB033 is supplied as a liquid drug product containing 200 mg/mL opicinumab in 20 mM L-histidine, 160 mM L-arginine hydrochloride, 10 mM L-methionine, 0.05% (w/v) polysorbate 80, pH 6.5. It is provided in glass vials, each containing 1000 mg BIIB033. BIIB033 is to be administered by IV infusion following dilution into saline as specified in the DHA.

The contents of the BIIB033 label will be in accordance with all applicable regulatory requirements. At a minimum, the study treatment label will include a study reference code, drug identifier, number of dosage units, lot number, expiry or use-by date, and other pertinent information in accordance with local law. The expiry or use-by date is also stored in the IRT system, and printable assignment reports are available to the unblinded pharmacist (or unblinded authorized designee). BIIB033 should not be used after the expiry or use-by date.

12.1.1. BIIB033 Preparation

The individual preparing BIIB033 should carefully review the instructions provided in the DHA and ensure the study blind is maintained.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or study treatment, do not use the study treatment. The vial in question should be saved at the study site and the problem immediately reported to Biogen.

12.1.2. BIIB033 Storage

Study treatment must be stored in a secure location.

BIIB033 vials are to be stored at 2°C to 8°C (36°F to 46°F) in a locked refrigerator with limited access. BIIB033 vials are to be protected from light, protected from freezing, and should not be shaken. If BIIB033 is frozen, the Sponsor should be notified immediately and the drug should be quarantined until further notice from the Sponsor.

For the most up-to-date storage requirements, follow the instructions provided in the DHA located in the Pharmacy Manual and Study Reference Guide.

12.1.3. BIIB033 Handling and Disposal

The unblinded pharmacist (or unblinded authorized designee) must return all used and unused vials of BIIB033 as instructed by Biogen unless approved for onsite destruction.

If any BIIB033 supplies are to be destroyed at the site, the institution or appropriate site personnel must obtain prior approval from Biogen, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BIIB033 Accountability

Accountability for study treatment is the responsibility of the unblinded pharmacist (or unblinded authorized designee). The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all vials both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made between the amount of BIIB033 supplied, dispensed, and subsequently destroyed or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Placebo and/or Comparator or Reference Product

The placebo (control agent) to be used in this study will be sterile normal saline (0.9% sodium chloride for IV administration). The manufacturer's directions for material storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the material.

13. EFFICACY, [redacted] ASSESSMENTS

See Section 5 for the timing of all assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, subjects will be asked to return to the clinic to have the evaluations repeated.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of BIIB033:

- EDSS
- T25FW
- 9HPT-D and 9HPT-ND (the right and left hands both tested, with the dominant hand tested before the nondominant hand)
- PASAT-3
- SDMT
- [redacted]

Refer to Table 1, Table 2, Table 3, and Table 4 for the timing of assessments.

[redacted]

[redacted]

[redacted]

14. SAFETY ASSESSMENTS

Refer to Section 5 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BIIB033:

- Medical history and prior MS treatment
- Continuous AE and SAE monitoring
- MS signs and symptoms (including relapses)
- Physical examination
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate
- Body weight measurements
- 12-Lead electrocardiograms (ECGs)
- C-SSRS
- Concomitant therapy and procedure recording

14.2. Laboratory Safety Assessments

Samples will be analyzed using Good Laboratory Practice-validated assays.

The following laboratory assessments will be performed to evaluate the safety profile of BIIB033:

- Hematology: complete blood count with differential and platelet count, and absolute neutrophil count. Prothrombin time, partial thromboplastin time, 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, ALT/SGPT, AST/SGOT, gamma-glutamyl-transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium, and follicle-stimulating hormone (FSH; for postmenopausal female subjects only).
- Urinalysis: blood, protein, and glucose (microscopic examination, if abnormal).
- Serum and urine pregnancy test (women of childbearing potential only).

[redacted]

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for SAE reporting (as defined in Section 15.1.3) and occurs after the subject signs the ICF but before administration of study treatment (BIIB033 or placebo).

15.1.2. Adverse Event

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

Determination of whether an abnormal laboratory value, vital sign result, and/or ECG result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE
- The result requires the subject to receive specific corrective therapy
- The result is considered by the Investigator to be clinically significant

15.1.3. Serious Adverse Event

An SAE is any untoward medical occurrence that:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important event

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

15.1.4. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.3 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.3.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

Note: AEs related to DMT use will not be considered "related" to the study treatment.

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

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

15.2.3. Severity of Events

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

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.

Severity of Event	
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the Investigator's Brochure for BIIB033.

15.3. Monitoring and Recording Events

15.3.1. Serious Pretreatment Events

A serious pretreatment event experienced by the subject after signing and dating the ICF, but before administration of study treatment (BIIB033 or placebo) is to be recorded on the SAE form. To report initial or follow-up information on an SAE, fax a completed SAE form; refer to the Study Reference Guide for complete contact information.

15.3.2. Adverse Events

In Part 1, any AE experienced by the subject between the time of first dose of study treatment and EOS Visit is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment. In Part 2, any AE collected between the signing of the ICF and EOS Visit is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the eCRF.

AEs that are ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will be recorded on the eCRF, as applicable.

15.3.3. Immediate Reporting of Serious Adverse Events

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

Reporting Information for SAEs
A report ***must be submitted*** to Biogen or designee regardless of the following: • Whether or not the subject has undergone study-related procedures • Whether or not the subject has received study treatment

- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, fax or email a completed SAE form; refer to the Study Reference Guide for complete contact information.

15.3.3.1. Deaths

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

15.3.4. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and EOS Visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen or designee within 24 hours as described in Section 15.3.3 . Follow-up information regarding an SAE also must be reported within 24 hours.

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

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

15.3.5. Suspected Unexpected Serious Adverse Reactions

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

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

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study or for 24 weeks after their last dose of study treatment (BIIB033 or placebo). If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

Any pregnancy that occurs between the first dose and 24 weeks after the last dose of study treatment (BIIB033 or placebo) must be reported. The Investigator must report a pregnancy by faxing the appropriate form to Biogen or designee within 24 hours of the study site staff becoming aware of the pregnancy. Refer to the Study Reference Guide for complete contact information. The Investigator or study site staff must report the outcome of the pregnancy to Biogen or designee. A pregnancy is not considered an AE and should not be recorded on the AE eCRF.

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

15.4.2. Overdose

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

15.4.3. Medical Emergency

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

15.4.3.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator can contact Biogen or designee to discuss such situations.

15.5. Contraception Requirements

All women of childbearing potential and all men must ensure that effective contraception is used during the study and for at least 24 weeks after their last dose of study treatment (BIIB033 or placebo). In addition, subjects should not donate sperm or eggs for the duration of the study and for at least 24 weeks after their last dose of study treatment.

For the purposes of this study, women who do not meet one of the following criteria are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
  - 12 continuous months of natural (spontaneous) amenorrhea without an alternative medical cause and a serum FSH level >40 mIU/mL
  - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, effective contraception is defined as use of one of the following:

For females:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected, or implanted hormonal methods of contraception
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.
- Sex with a male who uses the methods described for males below.

For males:

- Vasectomy with negative semen analysis at follow-up, or the use of condoms with spermicide.
- Sex with a female who uses the methods described for females if she is of childbearing potential.

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence

(e.g., calendar, ovulation, symptothermal, and postovulation methods) and withdrawal are not considered acceptable methods of contraception.

For DMTs, contraceptive requirements per label must be followed.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the eCRF regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event. Follow up on any ongoing SAE until the event has resolved, stabilized, or returned to baseline status.
- Monitor and record all pregnancies and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and fax it to Biogen or designee within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen or designee within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the eCRF, as applicable.
- Report SAEs to local ethics committees, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before a site can enroll any subjects, the Clinical Monitor is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

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

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The Part 1 and Part 2 objectives/endpoints are listed in Section 6 Table 5 and Table 6, respectively.

16.1. Demography and Baseline Disease Characteristics

Demographic and baseline disease characteristic data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, interquartile range, and overall range) for continuous variables or with number and percentages for categorical variables.

16.2. Efficacy

16.2.1. Analysis Population

The efficacy endpoints will be analyzed for the ITT population. The ITT population includes all randomized subjects who receive at least 1 dose of study treatment. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Methods of Analysis

Data will be collected and analyzed in 2 phases:

1. After the Part 1 placebo-controlled phase is completed, the efficacy and safety analysis will be performed. All data will be summarized by treatment group (BIIB033 750 mg and placebo).

2. Analyses will be performed as needed during the Part 2 OLE. Descriptive statistics will be used to evaluate the long-term safety and efficacy data of BIIB033.

Summary statistics will be presented. For continuous endpoints, the summary statistics will generally include the number of subjects with data, mean, SD, median, interquartile range, and overall range. For categorical endpoints, the summary statistics will generally include the number of subjects with available data and the percent of subjects with data in each category.

In the analysis of Part 1 efficacy variables, comparisons will be made between the active dose group (BIIB033 750 mg) versus the placebo group.

16.2.2.2. Analysis of the Primary Endpoint in Part 1

The primary efficacy endpoint of Overall Response Score will be summarized using descriptive statistics by treatment groups and visits. A Mixed Model for Repeated Measures (MMRM) will be used as the primary analysis to analyze the Overall Response Score up to week 72. Treatment, visit, treatment by visit interaction, baseline component measurements (EDSS, T25FW, 9HPT),

and stratification factors will be included in MMRM as fixed effects. The primary hypothesis test for treatment comparison (BIIB033 750 mg versus placebo) will be based on the main effect over 72 weeks derived from the model. If the main effect is significant at an α level of 0.05 (2-sided), treatment difference at individual timepoints (visits) will also be assessed based on the same model. Subgroup analyses will be performed as supportive analyses with subgroups defined a priori in the statistical analysis plan.

16.2.2.3. Analysis of the Secondary Endpoints in Part 1

Treatment comparison with respect to secondary endpoints will be made in sequential order for the endpoints listed in Section 6. The proportion of patients with confirmed improvement will be analyzed using logistic regression. The time from randomization to confirmed improvement will be analyzed using the Cox proportional hazards model. Where appropriate, baseline component measurements (EDSS, T25FW, 9HPT-D, 9HPT-ND, PASAT-3, and SDMT) and stratification factors will be included in both logistic regression and Cox model as covariates. The odds ratio from logistic regression and the hazard ratio from the Cox model will be derived with 95% confidence interval.

[redacted]

16.2.2.5. Analysis of Endpoints in Part 2

Descriptive statistics will be used to evaluate the long-term safety and efficacy data of BIIB033. Additional analyses of the efficacy endpoints for combined data from Part 1 and Part 2 may be performed based on randomization treatment group in Part 1. Additional analyses of Part 2 efficacy endpoints may be performed by using Part 1/Day1 as baseline for all subjects. The statistical methods will be specified in detail in the statistical analysis plan.

[redacted]

[redacted]

16.4. Safety

16.4.1. Analysis Population

For Part 1, the safety population is defined as all subjects who receive at least 1 dose of study treatment in Part 1.

For Part 2, the safety population is defined as all subjects who receive at least 1 dose of study treatment in Part 2.

16.4.2. Methods of Analysis

All AEs, clinical laboratory abnormalities, vital signs, physical examinations, ECG, MS signs and symptoms, and C-SSRS will be evaluated for safety.

16.4.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be summarized. Treatment emergent is defined as having an onset date that is on or after the first dose of double-blind treatment, or as worsening after the first dose of double-blind treatment.

The incidence of clinical TEAEs will be summarized by treatment group, severity, and by relationship to the study treatment. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities.

16.4.2.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology, blood chemistry, and urinalysis. Laboratory data will be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters and shifts from baseline to high/positive status for urinalysis will be presented. Also, summaries of laboratory values categorized based on potentially clinically significant abnormalities will be created. Summary statistics for actual values and change from baseline will be presented for quantitative laboratory data.

16.4.2.3. Vital Signs

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

The definitions of these clinically relevant abnormalities are shown in Table 7.

Table 7: Criteria Used 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

16.4.2.4. Physical Examinations

Clinically significant abnormal findings will be reported as AEs and included in the AE analyses.

16.4.2.5. Electrocardiogram

The number and percentage of subjects with shifts to the categorical values (abnormal not AE, or abnormal AE) will be summarized by treatment group.

16.4.2.6. Multiple Sclerosis Signs and Symptoms

The changes from baseline will be summarized by treatment group.

16.4.2.7. Columbia Suicide Severity Rating Scale

The C-SSRS data will be summarized by treatment group.

16.5. Immunogenicity Data

16.5.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 postdose immunogenicity sample collected.

For Part 1, the analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 postdose immunogenicity sample collected.

For Part 2, samples will only be collected and stored. Immunogenicity assessment may be performed at sponsor's discretion.

16.5.2. Methods of Analysis

The incidence of anti-BIIB033 serum antibodies will be summarized by treatment group.

16.6. Interim Analyses

In Part 1, an interim analysis 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. The futility criteria will be specified in detail in the statistical analysis plan. This study may be terminated early if the prespecified futility criteria are met at interim analysis. The study management team, Investigators, and subjects will remain blinded. The analyses to be performed when Part 1 is completed are not considered as interim analysis.

In Part 2, interim analysis 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.

16.7. Sample Size Considerations

In Part 1, a sample size of 120 subjects per treatment group will have approximately 80% power to detect a true mean treatment difference of 0.354 in the main effect of Overall Response Score over 72 weeks. 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 mean difference of 0.354 between the 2 treatment groups is based on the 90% one-sided lower confidence bound of the estimated treatment difference 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.

17. ETHICAL REQUIREMENTS

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

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites in countries other than the United States.

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

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

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

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

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

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including Screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject

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

Written informed consent must be obtained from subjects electing to enroll in Part 2 before any Part 2 assessments are performed.

[redacted]

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected and will be used during analysis of study results (unless not permitted by local law).

A copy of the signed and dated ICF must be given to the subject. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

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

17.4. Subject Data Protection

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

During the study, subjects' race and ethnicity will be collected (unless not permitted by local law). These data will be used in the analysis of the safety and/or [redacted] of the study treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity.

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

17.5. Compensation for Injury

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

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

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

18.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate.

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

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Clinical Monitor will visit the study site at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on subject safety, data integrity, and critical data and processes.

During these visits, eCRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Documentation of results will be provided to Biogen or designee in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of subject rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

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

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

Biogen will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

19.1.1. Contract Research Organization

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

19.1.2. Interactive Response Technology

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

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on eCRFs by a web-based electronic data capture (EDC) tool developed by a CRO and configured by the EDC vendor. PROs will be completed by the subject on paper forms and subsequently entered into the EDC tool by site staff.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Biogen to analyze all blood chemistry, hematology, and urine samples collected for this study. [redacted] and other samples will be analyzed at a laboratory selected by Biogen.

[redacted]

19.2. Study Committees

19.2.1. Independent Data Monitoring Committee (Part 1 Only)

An independent data monitoring committee (IDMC) will be formed to review ongoing safety data during the course of Part 1 only. A charter will be written for this IDMC.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

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

In the event of a protocol modification, the ICF may require similar modifications (see Section 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

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

19.5. Retention of Study Data

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

19.6. Study Report Signatory

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

Biogen will follow all applicable local regulations pertaining to study report signatories.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

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

_____

Investigator's SignatureDate

_____

Investigator's Name (Print)

_____

Study Site (Print)

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AMENDMENT SUMMARY

Biogen Protocol 215MS202

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

Version 3

Date: 13 February 2019

EUDRA CT Number: 2017-001224-22

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

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 215MS202 is to add an optional open-label extension (OLE) phase (Part 2) that will investigate the long-term safety and efficacy of BIIB033 treatment as an add-on therapy to anti-inflammatory disease-modifying therapies (DMT) for approximately 2 years (96 weeks). [redacted]

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

Section 7.1, Study Overview

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, ~~A~~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 (as defined in Section 4.4) and will continue taking their DMT throughout the study.

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

- Screening (pretreatment)
- Treatment Period: 1 visit every 4 weeks between Baseline/Day 1 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 ~~T~~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**.

Section 7.2, 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 who enroll in Part 2 do not need to have the 12-week postdose follow-up (EOS); 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 up to approximately 188 weeks.

Section 7.2.1, Screening

For Part 1, S~~s~~ubject eligibility for the study will be determined at Screening within 28 days prior to Day 1/Baseline.

For subjects participating in Part 2, Part 1/Week 72 will be the combined final Part 1 Visit and the Part 2 Screening Visit. In case the Part 2 Screening Visit is unable to be performed at Part 1/Week 72, a separate visit may occur within 4 weeks prior to Part 2/Day 1 (see Section 5.3).

Section 7.2.2, Treatment Period

Part 1

Study treatment with BIIB033 or placebo will be initiated on Day 1 after all baseline assessments are completed.

The Treatment Period will consist of 19 study visits beginning with Day 1/Baseline and then every 4 weeks at Weeks 4 through Week 72 with a visit window of ±5 days (see Section 5).

Subjects **who do not enroll in Part 2** will return to the study site for a post-treatment EOS Visit at Week 84, 12 weeks±10 days after the last dose of BIIB033 or placebo.

Part 2

Study treatment with BIIB033 will be initiated on Day 1 after all Part 2/Day 1 assessments are completed.

The Treatment Period will consist of 25 study visits beginning with Day 1 and then every 4 weeks at Weeks 4 through Week 96 with a visit window of ±5 days (see Table 3 and Table 4).

⋮

Section 7.2.4, Follow-Up *(new section)*

Part 1

Subjects who enroll in Part 1 but not Part 2 will return to the study site for an End of Part 1 Evaluation approximately 12 weeks after the last dose of study treatment (Part 1/Week 72 Visit). Subjects who enroll in Part 2 do not need to have the Part 1 12-week postdose follow-up (EOS) Visit.

Part 2

Subjects will return to the study site for a post-treatment EOS Visit at Week 108, 12 weeks±10 days after the last dose of BIIB033.

Section 7.3, Responsibilities of Study Site Personnel

For each subject **in Part 1 and Part 2**, the Principal Investigator of the site will designate the following investigational site personnel:

⋮

The *examining technician* (or the examining neurologist) will be responsible for the following:

- Administering the Timed 25-Foot Walk (T25FW), 9HPT-D, 9HPT-ND, 3-Second Paced Auditory Serial Addition Test (PASAT-3), Symbol-Digit Modalities Test (SDMT), ~~and~~ [redacted] at each scheduled timepoint required in the protocol

- These guidelines must be strictly followed:

  – The *examining technician* must remain blinded to AEs, concomitant medications, laboratory data, [redacted], and any other data that have the potential of revealing the treatment assignment.

  – To ensure consistency across sites, *examining technicians* must undergo a standardized training session prior to enrollment of subjects at their site.

  – All sites should attempt to maintain the same *examining technician* throughout the study.

  – If an *examining technician* has to be replaced, the new *examining technician* must undergo a training session prior to performing any study assessment.

[redacted]

The unblinded *pharmacist* (or unblinded authorized designee) will be responsible for the following:

- Receipt, storage, distribution, and accountability of study treatment

- Storage and security of unblinding documentation related to study **treatment**~~drug~~, dose preparation, and study **treatment**~~drug~~ assignment. All treatment assignment or study **treatment**~~drug~~ preparation information must be maintained strictly confidential at all times. Measures to prevent inadvertent unblinding must be followed.

- Preparation of study **treatments**~~drugs~~ for IV infusion

Section 7.4, Study Stopping Rules

For Part 1 and Part 2 of the study, Biogen may terminate this study at any time, after informing Investigators. Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

Rationale: The purpose of the optional OLE/Part 2 of Protocol 215MS202 is to investigate the long-term safety and efficacy of BIIB033 treatment as an add-on therapy to anti-inflammatory DMTs for approximately 2 years (96 weeks). [redacted] Addition of the OLE will provide the following:

- The OLE allows for a more thorough assessment of safety due to longer exposure to BIIB033, i.e., approximately 3.5 years of safety data for approximately half of the subjects treated with BIIB033 (subjects treated with BIIB033 in Part 1), and the other half (subjects treated with placebo in Part 1) will have approximately 2 years of safety data.
- Long-term efficacy assessments will help determine whether efficacy is sustained over time and allows for both assessment of long-term neuroprotective effects and long-term differentiation among patients on differing DMTs.
- [redacted]
- [redacted]

This change also affects the following sections:

- Section 4.4.2, Rationale for Part 2: Open-Label Extension
- Section 4.5, Rationale for Dose and Schedule Selection
- Section 5.1, Study Schematics *(new Figure 2)*
- Section 5.2, Part 1 – Schedule of Activities
- Section 5.3, Part 2 – Schedule of Activities *(new Table 3 and Table 4)*
- Section 6.1, Part 1 Objectives and Endpoints
- Section 6.2, Part 2 Objectives and Endpoints *(new Table 6)*

- Section 8.1, Inclusion Criteria – Part 1
- Section 8.2, Exclusion Criteria – Part 1
- Section 8.3, Inclusion Criteria – Part 2 *(new section)*
- Section 8.4, Exclusion Criteria – Part 2 *(new section)*
- Section 9.1, Screening and Enrollment
- Section 9.2, Randomization
- Section 9.3, Blinding Procedures
- Section 10.1, Discontinuation of Study Treatment
- Section 10.3, Withdrawal of Subjects From Study
- Section 11.1.1, BIIB033 and Placebo
- Section 11.5.1.1.1 Background Anti-Inflammatory DMTs for Use with Study Treatment
- Section 11.5.1.1.2, Other Allowed Concomitant Therapy
- Section 13.1, Clinical Efficacy Assessments
- [redacted]
- [redacted]
- [redacted]
- Section 16.2, Efficacy
- [redacted]
- Section 16.4.1, Safety Analysis Population
- Section 16.5, Immunogenicity Data
- Section 16.6, Interim Analyses
- Section 16.7, Sample Size Considerations
- Section 17.3, Subject Information and Consent

- [redacted]
- Section 19.2.1, Independent Data Monitoring Committee (Part 1 Only)

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 1, Synopsis

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

Section 5.2, Part 1 - Schedule of Activities

Change: In footnote 19 to Table 1, the interval between natalizumab infusion and BIIB033 or placebo infusion was changed from a minimum of 2 hours to a minimum of 1 hour if given on the same day.

Now reads:

[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 ~~2~~ **1-hour** interval between infusions. If any infusion reaction occurs with natalizumab, the infusion of BIIB033 should not be administered on that same day.

Rationale: This change was made for consistency with the established 1-hour observation period performed after natalizumab infusion, as described in the United States Prescribing Information and European Union Summary of Product Characteristics.

This change also affects Section 5.2, Part 1 – Schedule of Activities, Table 2, footnote 19; and Section 11.5.1.1.1, Background Anti-Inflammatory DMTs for Use with Study Treatment.

Section 11.5.1.1.2, Other Allowed Concomitant Therapy

Change: Medical marijuana was added as an allowed treatment of MS symptoms.

Now reads:

- Medications used to treat MS symptoms, such as spasticity, bladder impairment, pain, or depression (such symptomatic therapy is not restricted, but should be optimized as early as possible during Screening in an attempt to maintain consistent treatment for the duration of the study). **Medical marijuana is allowed for treatment of MS symptoms if it is consistent with local MS treatment guidelines and local regulations, is maintained on a stable regimen for at least 30 days prior to Part 2/Day 1, and throughout the study.**

Rationale: Although MS symptomatic medications are allowed, there have been questions from sites about whether medical marijuana is allowed as concomitant medication. This change clarifies the scope of allowed medical marijuana treatment for this study.

Section 15.5, Contraception Requirements

Change: Barrier methods of contraception with use of a spermicide were added as effective contraception for female subjects.

Now reads:

- **Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.**

Rationale: BIIB033 showed no evidence of teratogenicity/fetotoxicity in nonclinical reproductive toxicology studies at all doses studied, and thus is unlikely to have a risk of human teratogenicity/fetotoxicity. Therefore, barrier methods of contraception with use of a spermicide were added to contraceptive requirements for female subjects for consistency with the definition of effective contraception and with the BIIB033 Investigator's Brochure.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected.
- The protocol title was updated throughout the document.
- The Sponsor signatory was updated.
- Section 2, List of Abbreviations, was updated.
- "Part 1," "Part 2," and corresponding subheadings were added throughout the protocol to distinguish the 2 different phases of the study.
- In Section 5.2, Part 1 – Schedule of Activities, the order of T25FW, 9HPT-D, 9HPT-ND, [redacted], and SDMT assessments before EDSS was clarified to align with site operational practice.
- [redacted]
- In Section 11.5.1.1.1, Background Anti-Inflammatory DMTs for Use with Study Treatment, text was added to clarify that the Medical Monitor should be notified of any DMT switches to ensure the necessary discussion on safety measures per label in the context of the study.
- In Section 11.5.1.2, Disallowed Concomitant Therapy, text was added to clarify exceptions to disallowed therapies.
- In Section 15.5, Contraception Requirements, text was added to clarify that contraceptive requirements for DMTs must be followed per label.
- In Section 16.2.2.5, Analysis of Endpoints in Part 2, text was added to clarify the baseline for additional analyses.

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AMENDMENT SUMMARY

Biogen Protocol 215MS202

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study 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

Version 2

Date: 14 June 2017

EUDRA CT Number: 2017-001224-22

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

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 215MS202 is to update to the safety reporting sections of the protocol for accurate representation of serious adverse event (SAE) and suspected unexpected serious adverse reaction reporting responsibilities.

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

Section 15.3.3, Serious Adverse Events

Now reads:

Any SAE experienced by the subject between the time of the signing of the ICF and EOS visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to ~~the~~ [redacted] ~~Medical Monitor~~**Biogen or designee** within 24 hours as described in Section 15.3.4. Follow-up information regarding an SAE also must be reported within 24 hours.

Rationale:

The contact details for reporting of SAEs were incorrect and were directing sites to submit SAEs to the "[redacted] Medical Monitor." This change was required to confirm SAEs are not sent to the [redacted] Medical Monitor.

This change also affects Sections 15.3.4, Immediate Reporting of Serious Adverse Events; 15.3.4.1, Deaths; 15.3.5, Suspected Unexpected Serious Adverse Reactions; 15.4.1, Pregnancy; 15.4.2, Overdose; 15.4.3.1, Unblinding for Medical Emergency; 15.6.1, The Investigator; and 15.6.2, Biogen.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 1, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol

Section 3, Sponsor Information

Change: To update to the safety reporting sections of the protocol for accurate representation of medical emergency reporting responsibilities.

Now reads:

For urgent medical issues in which the [redacted] **study's** Medical ~~Monitor~~**Director** should be contacted, please refer to the Study Reference Guide for complete contact information.

Rationale:

The contact details for reporting urgent medical issues were not accurately defined. This change was required to define urgent medical issues accurately, and the sites should refer to the Study Reference Guide for complete contact information.

Section 8.1, Inclusion Criteria

Change: To update to the inclusion criterion regarding donation of sperm or eggs.

Now reads:

All female subjects of childbearing potential and all male subjects must practice effective contraception during the study and be willing and able to continue contraception for at least 24 weeks after their last dose of study treatment (BIIB033 or placebo). In addition, subjects should not donate sperm or eggs during the study and for at least ~~90 days~~ **24 weeks** after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.

Rationale:

The inclusion criterion regarding donation of sperm or eggs was updated to at least 24 weeks to align with the requirement for effective contraception (i.e., 24 weeks after last dose of study treatment [BIIB033 or placebo]).

This change also affects Section 15.5, Contraception Requirements.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- The Sponsor signatory was updated.
- Section 4.3.2, Clinical Experience, was updated to reflect that 1% of BIIB033-treated subjects experienced hypersensitivity reactions in Study 215MS201.
- Section 5, Study Schematic and Schedule of Activities, Table 2: Study Activities (Week 56 to Week 84), was updated [redacted]
- Section 7.3, Responsibilities of Study Site Personnel, was updated to reflect that physician assistants who meet the criteria may function as examining neurologists in this study after receiving Sponsor or designee's approval.
- Section 16.2.2.3, Analysis of the Secondary Endpoints, was updated to remove the analysis of 'confirmed worsening' as this is not included as a secondary endpoint.
- Typographical errors and formatting were corrected.