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PROTOCOL NUMBER: 215ON203 / NCT02657915

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201

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SPONSOR SIGNATURE

Protocol 215ON203 was approved by:

[redacted]

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Biogen MA Inc.

9th June 2016

Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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

2. LIST OF ABBREVIATIONS

9HPT	9-Hole Peg Test
AE	adverse event
ANCOVA	analysis of covariance
AON	acute optic neuritis
CDMS	clinically definite multiple sclerosis
CI	confidence interval
CIS	clinically isolated syndrome
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
[redacted]	[redacted]
EDSS	Expanded Disability Status Scale
FITC-BIIB033	fluorescein isothiocyanate-conjugated BIIB033
FF-VEP	full-field visual evoked potential
[redacted]	[redacted]
GCP	Good Clinical Practice
Gd	gadolinium
IB	Investigator's Brochure
IP	Investigational product
HCVA	high-contrast visual acuity
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN-β	interferon-beta
IgG1	immunoglobulin G1
ITT	intent-to-treat
IV	intravenous
LCLA	low-contrast letter acuity
MAD	multiple-ascending dose
MFD	maximum feasible dose
[redacted]	[redacted]
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite
[redacted]	[redacted]
NEI-VFQ-25	25-item National Eye Institute Visual Function Questionnaire
[redacted]	[redacted]

PASAT	(3-Second) Paced Auditory Serial Addition Test
PK	pharmacokinetic(s)
RGCL	retinal ganglion cell layer
RNFL	retinal nerve fiber layer
[redacted]	[redacted]
RRMS	relapsing-remitting multiple sclerosis
SAD	single-ascending dose
SAE	serious adverse event
SC	subcutaneous
[redacted]	[redacted]
SDMT	Symbol-Digit Modalities Test
SPMS	secondary progressive multiple sclerosis
SUSAR	suspected unexpected serious adverse reaction
T25FW	Timed 25-Foot Walk

3. SYNOPSIS

Protocol Number:	215ON203
Protocol Title:	A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201
Version Number:	4.0
Study Indication:	Acute optic neuritis (AON)
Study Rationale:	BIIB033 (human anti-LINGO-1 monoclonal antibody) is an investigational product with the potential of enhancing remyelination and neuroaxonal protection. In Study 215ON201, treatment of patients with AON with BIIB033 displayed evidence of functional remyelination in the affected eye by demonstrating significant improvement in visual evoked potential latency over treatment with placebo. The electrophysiologic differences between the treatment and placebo groups were first observed at Week 12 during the dosing period and persisted throughout the subsequent monthly dosing visits. More interestingly, this trend continued for an additional 3 months through the Follow-Up Visit at Week 32 despite subjects completing the dosing period at Week 20. Study 215ON201 also showed that all subjects, regardless of assigned treatment, recovered clinically to a large extent regardless of treatment assignment or severity of injury to the retina or the optic nerve; however, not all subjects demonstrated complete functional recovery upon electrophysiologic examination. The rationale for the discrepancy between clinical recovery and electrophysiological improvement is unclear and requires further investigation. Given these data, the proposed follow-up study is necessary to assess the long-term electrophysiologic and clinical outcomes of this patient population with past randomized exposure to remyelinating therapy versus placebo and also to explore potential mechanism(s) by which patients recover

	from previous AON. This information will be critical in ongoing clinical development of remyelinating therapies so that they can be optimally evaluated and utilized for maximal benefit.
Phase of Development:	2
Study Objectives and Endpoints:	The primary objective of this study is to assess full-field visual evoked potential (FF-VEP) latency in subjects who were enrolled in Study 215ON201 at 2 years (+ up to 12 months) after the last study visit. The primary endpoint that is related to this objective is the change in FF-VEP latency of the affected eye as compared to the baseline of the fellow eye at 2 years (+ up to 12 months) after the last study visit assessment (Week 32 or projected Week 32 visit) in Study 215ON201. The secondary objective is to assess clinical progression and severity of central nervous system (CNS) demyelinating disease in subjects who were enrolled in Study 215ON201 at 2 years (+ up to 12 months) after the last study visit. The endpoints that relate to this objective are as follows: • Evaluate incidence of clinically definite multiple sclerosis (CDMS) and time to diagnosis of CDMS. • Evaluate severity of CNS demyelinating disease with Expanded Disability Status Scale (EDSS), Symbol-Digit Modalities Test (SDMT), and multiple sclerosis functional composite (MSFC). The MSFC includes the following: – Timed 25-Foot Walk (T25FW) – 9-Hole Peg Test (9HPT) [dominant and nondominant hands] – (3-Second) Paced Auditory Serial Addition Test (PASAT) • Evaluate change in disease activity from baseline with brain magnetic resonance imaging (MRI)

	with and without gadolinium (Gd). MRI analysis will include the following: – Number of Gd-enhanced lesions – Volume of T2 lesions [redacted]
Study Design:	This is a blinded, multicenter, follow-up study to determine the long-term electrophysiologic and clinical outcomes in subjects previously enrolled in Study 215ON201. One group is planned, with eligible subjects (previously enrolled in Study 215ON201) having been already administered at least 1 study treatment (BIIB033 100 mg/kg or placebo) by intravenous infusion once every 4 weeks for 20 weeks (a total of 6 doses). Dosing was completed 2 years (+ up to 12 months) prior to enrollment in this follow-up study. No additional study drug or placebo will be administered.
Study Location:	Approximately 33 sites globally are planned.
Number of Planned Subjects:	A maximum of 82 subjects will be eligible for enrollment (determined from the number of subjects who received at least 1 dose of BIIB033 100 mg/kg or placebo in Study 215ON201).
Study Population:	This study will be conducted in subjects who have participated in and received at least 1 dose of BIIB033 or placebo in Study 215ON201. Detailed criteria are described in Section 8.
Duration of Follow-up:	Eligible subjects will be enrolled at 2 years (+ up to 12 months) after their last study visit (Week 32 or projected Week 32 visit) if the subject did not complete all visits in Study 215ON201. Enrollment in Study 215ON203 will end no later than approximately 2 years after the last patient's Week 32 visit (or projected Week 32 visit) in the parent study, Study 215ON201. Subjects will perform 1 set of follow-up assessments at this timepoint.

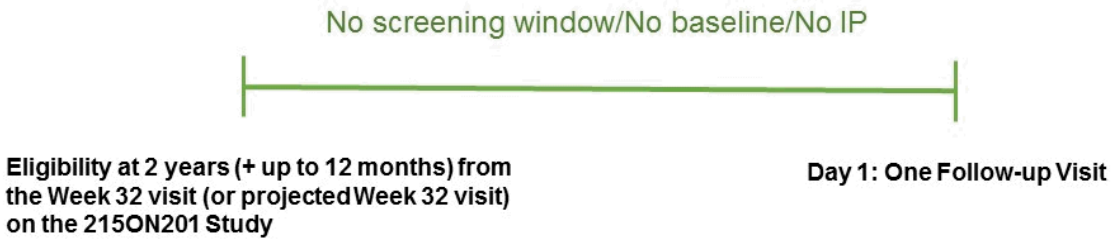
Evaluations:	
Safety:	Assessments evaluating the safety profile will include physical examinations, vital sign measurements, and adverse events (AEs)/serious adverse events (SAEs). Any AE or SAE experienced by the subject after informed consent form sign-off through the end-of-study visit is to be recorded on the case report form or SAE form, respectively, regardless of the severity of the event or its relationship to study procedure(s) and/or to prior treatment with investigational drug (administered in Study 215ON201). Subjects will be followed for all SAEs until the event has resolved, stabilized, or returned to baseline status.
Statistical Analysis Methods:	The primary analysis will be on the change in FF-VEP latency of the affected eye as compared to the baseline (measured prior to dosing in Study 215ON201) of the fellow eye at 2 years (+ up to 12 months) after the last study visit assessment (Week 32 or projected Week 32 visit) in Study 215ON201. The ANCOVA model will be used to test the difference between the 2 original treatment groups from Study 215ON201, adjusting for the baseline of the unaffected fellow eye. The secondary endpoints will include the time to diagnosis of CDMS; severity of disease evaluated by EDSS, SDMT, and MSFC (including T25FW, 9HPT, and PASAT); and brain MRI results. Number and percentage of subjects with diagnosis of CDMS will be summarized, and descriptive statistics of time to diagnosis of CDMS will be presented. EDSS, SDMT, MSFC, and brain MRI outcomes will also be summarized using descriptive statistics. Statistical testing for efficacy endpoints will be made between the BIIB033 group and the placebo group. There will be no multiple comparison adjustments. Unless stated otherwise, all statistical tests will be 2-sided with statistical significance level of 0.05. [redacted]

Interim Analysis:	An interim analysis will be performed when approximately 50% of potentially projected available subjects have been enrolled into the study to provide information to assist the interpretation and design of ongoing clinical development of BIIB033 and other potential CNS remyelinating therapies. Given that there is no intervention in this study, study stoppage does not apply. No stopping or continuation rules will be applied for the interim analysis.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 215ON203

4.1. Study Schematic

Figure 1: Study Design



IP = investigational product.
Note: All assessments should be performed on the same day where possible or within a +5-day window of the 1-day visit.

4.2. Schedule of Activities

Table 1: Schedule of Activities

Tests and Assessments[1]	**Day 1**[2]**:** **(2 Years + up to 12 Months After Week 32 Visit in Study 215ON201 or Projected Week 32 Visit if the Subject Did Not Complete All Visits)**
Informed Consent	X
Eligibility Criteria Check	X
Medical History[3]	X
Multiple Sclerosis Diagnosis	X
Multiple Sclerosis Signs and Symptoms	X
Concomitant Therapy and Procedures Recording	X
Vital Signs[4]	X
Physical Examination	X
Expanded Disability Status Scale[5]	X
Symbol-Digit Modalities Test	X
Multiple Sclerosis Functional Composite Including • Timed 25-Foot Walk • 9-Hole Peg Test (Dominant and Nondominant Hands) • (3-Second) Paced Auditory Serial Addition Test	X
[redacted]	

Tests and Assessments[1]	**Day 1**[2]**:** **(2 Years + up to 12 Months After Week 32 Visit in Study 215ON201 or Projected Week 32 Visit if the Subject Did Not Complete All Visits)**
[redacted]	
Full-Field Visual Evoked Potential[7]	X
[redacted]	
Adverse Event/Serious Adverse Event Recording[12]	X

[redacted] MRI = magnetic resonance imaging.

[1] All assessments should be performed on the same day and in the order listed, when possible (or within a +5-day window of the 1-day visit).

[2] Completion of the Day 1 visit assessments constitutes the end-of-study visit.

[3] Medical history will be taken from after last study visit in Study 215ON201.

[4] Vital signs include temperature, systolic and diastolic blood pressure, pulse rate, body weight, and respiratory rate (after sitting for at least 5 minutes).

[5] Expanded Disability Status Scale should be performed by a study certified rater. Where applicable, refer to study manual for instructions.

[6] [redacted]

[7] Sites and technicians must be qualified and approved by the central reader to perform [redacted], full-field visual evoked potential, and [redacted].

[redacted]

[12] Adverse event/serious adverse event monitoring will be recorded after informed consent form sign-off through the end-of-study visit.

5. INTRODUCTION

BIIB033, a first-in-class human monoclonal antibody directed against LINGO-1, is a negative regulator of myelination and axonal growth. Antagonizing LINGO-1 with BIIB033 has the potential to enhance remyelination and neuroaxonal protection in the central nervous system (CNS).

LINGO-1 is a cell surface glycoprotein that is selectively expressed in the adult CNS in neurons and oligodendrocytes [Barrette 2007; Carim-Todd 2003; Llorens 2008; Mi 2004; Park 2005; Shao 2005]. It functions as a negative regulator of oligodendrocyte differentiation, myelination, and remyelination [Lee 2007; Mi 2005; Mi 2009; Mi 2008]. Axonal and neuronal expression of LINGO-1 increases after injury [Ji 2006; Mi 2004]. LINGO-1 expression prevents myelination of axons by oligodendrocytes.

Several nonclinical studies have demonstrated the potential for LINGO-1 antagonism to enhance CNS remyelination and neuroaxonal protection in animal models of toxic (cuprizone plus rapamycin) [Mi 2009], chemical (lysophosphatidylcholine), and inflammatory (myelin oligodendrocyte glycoprotein-experimental autoimmune encephalomyelitis) [Mi 2007] demyelination and of toxic (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) neuronal [Inoue 2007] and traumatic/hypertensive optic nerve [Fu 2008] and spinal cord [Ji 2008; Ji 2006] injury. The leading hypothesis for this clinical development program is that antagonism of LINGO-1 with BIIB033 will enhance remyelination and neuroaxonal protection in CNS demyelinating diseases such as multiple sclerosis (MS) and acute optic neuritis (AON), leading to CNS improvement with corresponding beneficial effects on neurological function and disability.

Additional details may be found in the BIIB033 Investigator's Brochure (IB).

5.1. Overview of Acute Optic Neuritis

The anterior visual pathway, particularly the optic nerve and its retinal nerve fiber layer (RNFL) and retinal ganglion cell layer (RGCL), is affected by AON and is a potential target for therapeutic compounds with properties to enhance remyelination and neuroaxonal protection. In a study of the long-term effects of AON in the context of MS, the RNFL was decreased to an average of 83 microns [Costello 2006; Talman 2010]. This corresponds to an average loss of ~20 microns or 20% of nerve fibers relative to unaffected eyes in patients with AON or to a loss of ~13 microns relative to eyes in patients with MS without history or presence of AON [Talman 2010]. Costello et al [Costello 2006] found that 74% of patients had 20% or greater thinning of the RNFL following AON. As also noted by Henderson et al [Henderson 2011 Aug], this RNFL thinning begins early (between 1 and 2 months after onset of AON), and nearly all of the eventual RNFL loss is complete by 6 months. This loss of RNFL is associated with a clinically important loss of visual function, as shown by a decrease of low-contrast letter acuity (LCLA) to an average of 21 letters out of 60 or a loss of 14 letters relative to unaffected MS eyes. There is also a permanent loss of visual motion perception in most patients affected by AON [Raz 2011].

Motion processing impairments in AON may be highly disruptive to the ability of patients to ambulate, drive, and navigate [Duffy 2011a; Duffy 2011b]. The permanent loss of visual function in AON is clinically important as reflected by a vision-related quality of life score of 84 on the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), which is 8 points lower than in unaffected patients [Balcer 2012]. This 8-point loss on the NEI-VFQ-25 is higher than the currently accepted 4-point threshold for clinically important changes in vision-related quality of life [Mowry 2009; Submacular Surgery Trials Research Group 2007].

5.2. Current Therapies for Acute Optic Neuritis

The only currently available treatment for AON is high-dose intravenous (IV) steroids (e.g., methylprednisolone) followed by an oral prednisone taper, which speeds up the recovery of symptoms (e.g., ocular pain) and high-contrast visual acuity (HCVA) primarily in the first 2 weeks after an attack, but has no long-term beneficial effects on the ultimate recovery of visual function [Beck 1992] nor is there evidence that it affects the degree of axonal loss or conduction velocity in the optic nerve pathway.

Despite treatment with high-dose steroids, over 60% of patients with AON are left with loss of visual function [Kupersmith 2007].

5.3. Overview of Multiple Sclerosis

MS is a chronic disabling neurological disease that affects an estimated 1 million people in North America and Western Europe. It is a disease of young adults, primarily women, with disease onset typically occurring between the ages of 20 and 40 years [Weinshenker 1989]. It is the most frequent cause of nontraumatic neurological disability affecting young adults in the Western world. Although the etiology is uncertain, evidence suggests that MS is, in part, an autoimmune disease directed against protein components of myelin. The diagnosis of clinically definite multiple sclerosis (CDMS) has traditionally been made on the basis of clinical criteria and requires that a patient experience at least 2 neurologic events consistent with demyelination, separated both in time and in location in the CNS [Poser 1983]. More recent diagnostic criteria have allowed for less than 2 neurologic attacks, when there is supportive laboratory evidence based on magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF) results [McDonald 2001]. The majority of patients with MS start out with a clinical course characterized by episodes or attacks (relapses) of neurologic dysfunction, which occur over many years. This phase of the disease is called relapsing-remitting multiple sclerosis (RRMS). Symptoms of such relapses include loss of vision or double vision, numbness or tingling sensation in the extremities, muscle weakness, slurred speech, difficulty with coordination, and bladder dysfunction. Patients having the first clinical attack are referred to as clinically isolated syndrome (CIS). The most common CIS types are AON, transverse myelitis, and brainstem attack. Patients with CIS with characteristic brain MRI lesions are considered to be having MS by the most recent diagnostic McDonald criteria [Polman 2011]. Patients with CIS without brain lesions are at low risk of developing MS. Early in the course of relapsing MS, the signs and symptoms tend to subside completely after each attack. Over time, there tends to be incomplete recovery from such attacks. The majority of patients with relapsing MS accumulate some

disability, and about half are unable to walk without assistance within 15 years of their initial diagnosis [Runmarker and Andersen 1993; Weinshenker 1989]. The majority of patients with RRMS eventually enter the secondary progressive phase of the disease (secondary progressive multiple sclerosis [SPMS]), characterized by steady worsening of disability independently of relapses. About 15% of the patients go into this progressive phase without prior development of a relapsing-remitting phase and are referred to as having a primary progressive MS.

5.4. Current Therapies for Multiple Sclerosis

Available therapies for the treatment of relapsing MS target the immunomodulation of inflammatory activity and include interferon-beta (IFN-β)1a, pegylated IFN-β1a, IFN-β1b, natalizumab, mitoxantrone, glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, and fingolimod. There is also 1 available symptomatic MS therapy to improve walking, prolonged-release fampridine, known as dalfampridine extended release in the United States.

5.5. Profile of Previous Experience with BIIB033

5.5.1. Nonclinical Experience

BIIB033 is a fully human aglycosylated immunoglobulin G1 (IgG1) monoclonal antibody that binds LINGO-1 with high affinity. As LINGO-1 is a cell surface glycoprotein selectively expressed in CNS oligodendrocytes and neurons that prevents myelination of axons by oligodendrocytes, a blockade of LINGO-1 may enhance remyelination and repair in CNS demyelinated lesions.

BIIB033 binds LINGO-1 with high affinity in humans, monkeys, rats, and mice; has high specificity for LINGO-1 and does not cross react with other LINGO family members; enhances differentiation of primary rat, monkey, and human oligodendrocytes in vitro; enhances axonal myelination in an in vitro rat dorsal root ganglion/oligodendrocyte precursor cell co-culture bioassay; has reduced Fcγ and complement effector functions compared to wild-type IgG1; and is efficacious in animal models using biochemical and functional readouts. These data suggest that BIIB033 will be an effective therapy to enhance remyelination in patients with MS.

An assessment of BIIB033 toxicology has been carried out in repeated-dose studies in rats and cynomolgus monkeys, as these species are considered pharmacologically relevant based on sequence homology with LINGO-1 and/or similarity in binding and in vitro functional activity with LINGO 1. Toxicology studies of up to 6 months in duration did not identify any adverse treatment-related effects or any effect on neurobehavioral assessments with weekly IV administrations of BIIB033 at up to a maximum feasible dose (MFD) of 316 mg/kg or 3-time-per week subcutaneous (SC) doses at up to 32 mg/kg. Effects on the CNS and respiratory system were transient, and none were considered adverse responses to BIIB033. In embryo-fetal toxicology studies in rats and rabbits, BIIB033 was shown to be not causing fetal abnormalities at maternal doses up to 316 mg/kg. Maternal toxicity and morbidity were noted in 1 rabbit given 316 mg/kg, but the relationship to BIIB033 treatment was unclear; no maternal toxicity was observed in rats at any dose.

Immunohistochemical analyses have identified target and nontarget antigen-specific cross-reactivity by fluorescein isothiocyanate-conjugated BIIB033 (FITC-BIIB033)-specific staining in a range of human, cynomolgus monkey, and rat tissues, including those of neural, epithelial, neuroendocrine, and connective tissue origins. Consistent BIIB033-specific immunostaining using 2 concentrations of FITC-BIIB033 was observed in the brain (primarily, the cerebral cortex) and spinal cord across all 3 species, and the pattern of FITC-BIIB033-specific staining was consistent with that of LINGO-1 protein localization, as previously observed in rodents. Additional non-neural tissues with inconsistent binding patterns across species were evaluated within the repeated-dose toxicology studies and were not identified as target organs of toxicity associated with BIIB033 administration up to an MFD dose over 6 months of treatment. The exposure-based safety margin for the highest dose planned for chronic dosing in the clinic (100 mg/kg/month) is projected to be 4- to 6-fold lower relative to exposures at the no-observed-adverse-effect level in toxicology species after 6 months of dosing.

Together, these data support ongoing evaluations of BIIB033 in Phase 2 studies.

See the IB for detailed information on nonclinical studies.

5.5.2. Clinical Experience

As of 07 May 2015, 72 healthy volunteers (54 BIIB033 and 18 placebo) have been dosed in a single-ascending-dose (SAD) clinical study (Study 215HV101), 47 subjects with MS (32 BIIB033 and 15 placebo) have been dosed in a multiple-ascending-dose (MAD) clinical study (Study 215MS101), 82 subjects with AON (41 BIIB033 and 41 placebo) have been dosed in a Phase 2 Study 215ON201, and 418 subjects with MS (treatment groups still blinded) have been dosed in the ongoing Phase 2 Study 215MS201.

Overall, BIIB033 has been well tolerated in clinical studies. In the completed Study 215HV101 (SAD), which evaluated the safety, tolerability, and pharmacokinetics (PK) of BIIB033 in healthy volunteers, doses ranging from 0.1 to 100 mg/kg BIIB033 were administered to a total of 54 healthy adult volunteers. There were no serious adverse events (SAEs) in the SAD study. Most adverse events (AEs) considered related to study treatment in the SAD study were mild, except for 3 moderate events (2 cases of headache and 1 case of gastroenteritis). The most common AEs with an incidence of ≥5% reported by subjects receiving BIIB033 were headache (10 subjects [19%]), upper respiratory tract infection (6 subjects [11%]), nasopharyngitis (4 subjects [7%]), and gastroenteritis (3 subjects [6%]). Overall, the frequency of AEs was similar between the BIIB033 and placebo groups.

In the completed Study 215MS101 (MAD), which evaluated the safety, tolerability, and PK of BIIB033 in subjects with RRMS or SPMS, multiple doses ranging from 0.3 to 100 mg/kg BIIB033 were administered to a total of 32 subjects. There were no SAEs in the MAD study. The frequency of AEs was similar in BIIB033-treated subjects compared with placebo-treated subjects. The most common AEs with an incidence of ≥5% reported by subjects receiving BIIB033 were headache and urinary tract infection (5 subjects [16%] each), upper respiratory

tract infection and MS relapse (3 subjects [9%] each), and postlumbar puncture headache (2 subjects [6%]).

The completed Phase 2 Study 215ON201 was designed to assess the efficacy, safety, tolerability, and PK of BIIB033 in subjects with their first episode of AON. In this study, the dose of 100 mg/kg BIIB033 was well tolerated, and the overall incidence of AEs was the same in the placebo and BIIB033 groups (34 subjects [83%] in each group). The most common AEs with an incidence of ≥10% reported by subjects receiving BIIB033 were nasopharyngitis (12 subjects [29%]), headache (11 subjects [27%]), fatigue (6 subjects [15%]), nausea (5 subjects [12%]), and paresthesia (4 subjects [10%]). There were 7 of 82 subjects (9%) who experienced SAEs, 5 subjects (12%) in the BIIB033 treatment group and 2 subjects (5%) in the placebo group. In the BIIB033 treatment group, 3 subjects had SAEs that were considered related to study treatment by the Investigator: 2 subjects with hypersensitivity reactions occurring during study treatment infusions and 1 subject with asymptomatic increased aspartate aminotransferase, increased alanine aminotransferase, and liver disorder. Two subjects in the BIIB033 treatment group experienced SAEs considered not related to study treatment. These included 1 subject with MS relapse and 1 subject with optic neuritis. All of the SAEs in the BIIB033 treatment group were reported as resolved. No anti-BIIB033 antibodies were seen in Study 215ON201, except for 1 subject who tested positive at predose baseline.

The reported events of hypersensitivity (serious and nonserious) in the clinical studies have occurred after the start of either the first or the second study treatment infusion in both Phase 1 and 2 studies. In all cases, the infusions were stopped, appropriate treatment was administered, and all events resolved.

The Phase 2 Study, 215MS201, was designed to assess the efficacy, safety, tolerability, and PK of BIIB033 in subjects with relapsing forms of MS when used concurrently with Avonex and is currently ongoing. In this study, the most common AEs with an incidence of ≥10% in the combined BIIB033 and placebo treatment groups are influenza like illness (175 subjects [42%]), MS relapse (123 subjects [29%]), headache (68 subjects [16%]), upper respiratory tract infection (51 subjects [12%]), urinary tract infection (46 subjects [11%]), pyrexia (44 subjects [11%]), and nasopharyngitis (40 subjects [10%]). Fifty of 418 subjects enrolled (12%) reported SAEs as of 07 May 2015. SAEs that were reported in more than 1 subject included MS relapse (27 subjects [6%]), urinary tract infection (3 subjects [<1%]), and hypersensitivity (4 subjects [<1%]). As this study is still ongoing, the treatment codes are blinded, and it is not known if the events occurred in subjects treated with BIIB033 or placebo.

BIIB033 PK following a single dose (IV and SC) up to 100 mg/kg in healthy volunteers and 2 repeated IV doses up to 100 mg/kg in subjects with MS was characterized in the SAD and MAD studies, respectively. BIIB033 PK appears to be similar between healthy volunteers and subjects with MS. In general, BIIB033 PK was linear with small volume of distribution at steady state, minimal target-mediated clearance, and an elimination half-life of approximately 2 to 3 weeks. As expected, the CSF/serum concentration ratio for BIIB033 in humans is estimated to be approximately 0.1%. In the Phase 2 Study 215ON201, the preliminary PK results suggest that

the predicted BIIB033 pharmacological exposure at 100 mg/kg was achieved in subjects with AON, and BIIB033 PK appears to be similar to healthy adults and subjects with MS.

Please refer to the BIIB033 IB for additional details and results on clinical studies.

5.6. Study Rationale

A biological effect of BIIB033 was shown in Study 215ON201 in subjects with AON. In this study, subjects received 6 doses of 100 mg/kg BIIB033 or placebo administered via IV infusion every 4 weeks up to Week 20, with Follow-Up Visits at Weeks 24 and 32. Efficacy results showed an improvement in mean change in full-field visual evoked potential (FF-VEP) latency values of the affected eye from the baseline of the fellow eye at Week 24 in the BIIB033 group compared with placebo in the intent-to-treat population (-3.48 [95% confidence interval (CI): -10.61, 3.65] msec, analysis of covariance [ANCOVA]). The treatment effect was more pronounced in the per-protocol population (-7.55 [95% CI: -15.12, 0.01] msec, ANCOVA). The electrophysiologic differences between the treatment and placebo groups, first observed at Week 12 during the dosing period, persisted throughout the subsequent monthly dosing visits.

The change in FF-VEP latency in the affected eye versus the baseline of the unaffected fellow eye by mixed model for repeated measures (MMRM) showed a greater treatment effect at Week 32 than at Week 24 for both the intent-to-treat (ITT) and per-protocol populations, despite subjects completing the dosing period at Week 20. In the ITT population, an improvement of -6.06 msec over placebo was seen in the BIIB033 group at Week 32 by MMRM ($p = 0.0711$). A significant improvement of -9.13 msec over placebo was seen in the BIIB033 group at Week 32 in the per-protocol population by MMRM ($p = 0.0112$).

Study 215ON201 also showed that all subjects, regardless of assigned treatment, recovered clinically to a large extend regardless of treatment assignment or severity of injury to the retina or the optic nerve; however, not all subjects demonstrated complete functional recovery upon electrophysiologic examination. The rationale for the discrepancy between clinical recovery and electrophysiological improvement is unclear and requires further investigation.

Given these data, the proposed follow-up study is necessary to assess the long-term electrophysiologic and clinical outcomes of this patient population with past randomized exposure to remyelinating therapy versus placebo, but also to explore potential mechanism(s) by which patients recover from previous AON. This information will be critical in the ongoing clinical development of remyelinating therapies so that they can be optimally evaluated and utilized for maximal benefit.

Please refer to the BIIB033 IB for additional details and results on Study 215ON201.

5.7. Rationale for Dosing Regimen

No study drug dosing is planned for this follow-up study.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to assess FF-VEP latency in subjects who were enrolled in Study 215ON201 at 2 years (+ up to 12 months) after the last study visit.

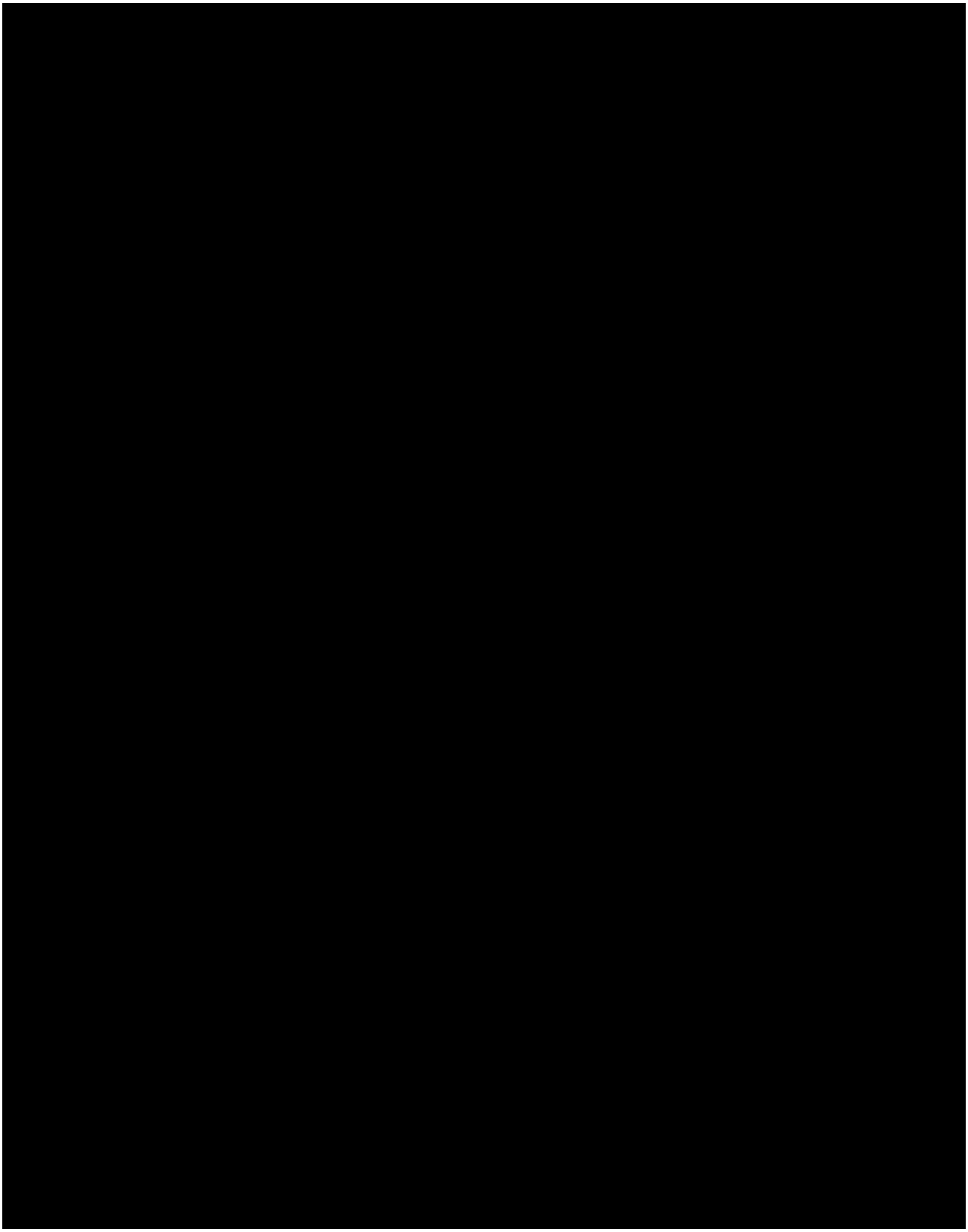
The primary endpoint that is related to this objective is the change in FF-VEP latency of the affected eye as compared to the baseline of the fellow eye at 2 years (+ up to 12 months) after the last study visit assessment (Week 32 or the projected Week 32 visit) in Study 215ON201.

6.2. Secondary Objectives and Endpoints

The secondary objective is to assess clinical progression and severity of CNS demyelinating disease in subjects who were enrolled in Study 215ON201 at 2 years (+ up to 12 months) after the last study visit.

The endpoints that relate to this objective are as follows:

- Evaluate incidence of CDMS and time to diagnosis of CDMS.
- Evaluate severity of CNS demyelinating disease with Expanded Disability Status Scale (EDSS), Symbol-Digit Modalities Test (SDMT), and multiple sclerosis functional composite (MSFC). MSFC includes the following:
  - Timed 25-Foot Walk (T25FW)
  - 9-Hole Peg Test (9HPT) [dominant and nondominant hands]
  - (3-Second) Paced Auditory Serial Addition Test (PASAT)
- Evaluate change in disease activity from baseline with brain MRI with and without gadolinium (Gd). MRI analysis will include the following:
  - Number of Gd-enhanced lesions
  - Volume of T2 lesions



7. STUDY DESIGN

7.1. Study Overview

This blinded, multicenter, follow-up study will determine the long-term electrophysiologic and clinical outcomes in subjects previously enrolled in Study 215ON201.

One group is planned, with eligible subjects (previously enrolled in Study 215ON201) having been already administered at least 1 study treatment (BIIB033 100 mg/kg or placebo) by IV infusion once every 4 weeks for 20 weeks (a total of 6 doses). Dosing was completed 2 years (+ up to 12 months) prior to enrollment in this follow-up study. A maximum of 82 subjects (determined from the number of subjects who received at least 1 dose of BIIB033 or placebo in Study 215ON201) will be included in this study. There is no formal sample size calculation. The number of subjects eligible for this study is determined by the number of subjects who participated in Study 215ON201.

See Figure 1 for a schematic of the study design.

7.2. Overall Study Duration

The study period will consist of an approximately 1-day visit (with a +5-day window of the 1-day visit) that is dependent on the scanner capabilities and equipment availability at each clinical site. Enrollment in Study 215ON203 will end no later than approximately 2 years after the last patient's Week 32 visit (or projected Week 32 visit) in Study 215ON201.

7.2.1. Screening

Subject eligibility for the study will be determined by the date of 2 years (+ up to 12 months) after the last study visit (Week 32) or projected Week 32 visit, if the subject did not complete all visits in Study 215ON201. There is no screening visit in this study.

7.2.2. Treatment

No study drug dosing is planned for this study.

7.2.3. Visit Schedule

Each subject will have approximately 1 scheduled study visit (with a +5-day window of the 1-day visit) that is dependent on the scanner capabilities and equipment availability at each clinical site.

7.3. Study Stopping Rules

Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

7.4. End of Study

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

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of Day 1 visit or at the timepoint specified in the individual eligibility criterion listed:

1. Must have participated in Study 215ON201 and received at least 1 dose of BIIB033 or placebo, as per protocol, within 2 years (+ up to 12 months) from Day 1 of this study (2 years from Week 32 or projected Week 32 visit, if the subject did not complete all visits in Study 215ON201).

2. 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.

8.2. Exclusion Criteria

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

1. Not previously enrolled in Study 215ON201.

2. Inability to comply with study requirements.

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

4. Subjects with recent kidney function, such as serum creatinine above upper limit of normal range, will not be allowed to receive administration of Gd but will otherwise be allowed to participate in the study, including MRI assessments not requiring the use of Gd.

5. Female subjects must have had a recent pregnancy test and must not be breastfeeding prior to MRI assessments with Gd.

9. ENROLLMENT AND REGISTRATION

9.1. Enrollment

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any study-related tests are performed (see Section 15.3). When a subject signs the informed consent form (ICF), that subject is considered to be enrolled 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 enrolment log.

9.2. Registration of Subjects

Subjects will be registered at 2 years (+ up to 12 months) after their last study visit (Week 32) or projected Week 32 visit, if the subjects did not complete all visits in Study 215ON201, and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2.

Refer to the Study Reference Guide for details on registration.

9.3. Blinding Procedures

This is a follow-up study with no investigational product. To maintain the blind from Study 215ON201, the treatment disclosure for Study 215ON201 will not be shared with sites or patients until the end of this study. Maintenance of the blind will reduce the risk of bias on the follow-up assessments.

10. WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Sponsor or Investigator for medical reasons or for noncompliance.

The reason for the subject's withdrawal from the study must be recorded in the subject's case report form (CRF).

11. FOLLOW-UP ASSESSMENTS

See Section 4 for the timing of all assessments.

11.1. One-Day Visit Assessments

This study will assess the electrophysiological function of the visual pathway using FF-VEP. The various electrophysiologic and imaging measurements will be made to assess feasibility of being utilized as potential clinical endpoints sensitive to remyelination therapy in multicenter clinical studies (Table 1). Clinical progression and severity of disease will be assessed by the following:

- Medical history, including date of diagnosis of CDMS
- MS diagnosis
- MS signs and symptoms
- Concomitant therapy and procedures recording
- Vital signs
- Physical examination
- EDSS
- SDMT
- MSFC (including T25FW, 9HPT, and PASAT)
- [redacted]
- [redacted]
- FF-VEP
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- AE and SAE recording

12. SAFETY ASSESSMENTS

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

12.1. Safety Assessments

The following safety assessments will be performed:

- Physical examinations
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, body weight, and respiratory rate
- AE and SAE recording

12.2. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The definitions of these clinically relevant abnormalities are shown in Table 2.

Table 2: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C
Pulse rate	>100 bpm <40 bpm
Systolic Blood Pressure	>160 mmHg <90 mmHg
Diastolic Blood Pressure	>100 mmHg <45 mmHg

bpm = beats per minute.

13. SAFETY DEFINITIONS, CLASSIFICATIONS, 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 must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

13.1. Definition

13.1.1. Adverse Event

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

13.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.

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

13.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
  - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 13.1.2 is met.

13.2. Safety Classifications

13.2.1. 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 13.1.2.
- The relationship of the event to the study procedure(s) and to prior treatment with investigational drug (administered in Study 215ON201) as defined in Section 13.2.2.
- The severity of the event as defined in Section 13.2.3.

13.2.2. Relationship of Events to Study Procedure(s) and Prior Treatment With Investigational Drug

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study procedure(s) and to prior treatment with investigational drug:

Relationship of Event to Study Procedure(s) and to Prior Treatment With Investigational Drug (Administered in Study 215ON201)	
Not related	An AE will be considered "not related" to the study procedure(s) and/or investigational drug (administered in Study 215ON201) if there is not a reasonable possibility that the event has been caused by the study procedure(s) and/or investigational drug. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between study procedure(s) and/or investigational drug and the event, the presence of a biologically implausible relationship between the study procedure(s) and/or investigational drug and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the study procedure(s) and/or investigational drug (administered in Study 215ON201) if there is a reasonable possibility that the event may have been caused by the study procedure(s) and/or investigational drug. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between study procedure(s) and/or investigational drug and the event, a known response pattern of the study procedure(s) and/or investigational drug, a biologically plausible relationship between the study procedure(s) and/or investigational drug and the AE, or a lack of an alternative explanation for the AE.

13.2.3. Severity of Events

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

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of study procedure(s); treatment for symptoms may be given and/or subject hospitalized.

13.2.4. Expectedness of Events

Expectedness of all AEs due to previous exposure to BIIB033 will be determined by Biogen according to the IB.

13.3. Monitoring and Recording Events

13.3.1. Adverse Events

Any AE experienced by the subject after ICF sign-off through the end-of-study visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study procedure(s) and/or to prior treatment with the investigational drug (administered in Study 215ON201).

13.3.2. Serious Adverse Events

Any SAE experienced by a subject after ICF sign-off through the end-of-study visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study procedure(s) and/or to prior treatment with the investigational drug (administered in Study 215ON201). SAEs must be reported to [redacted] within 24 hours as described in Section 13.3.3. Follow-up information regarding an SAE also must be reported within 24 hours.

Subjects will be followed for all SAEs until the event has resolved, stabilized, or returned to baseline status.

13.3.3. 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 [redacted] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs
Any SAE that occurs after ICF sign-off through the end-of-study visit must be reported to [redacted] within 24 hours of the study site staff becoming aware of the event. After the end-of-study visit, the SAE should only be reported if the Investigator considers it related to investigational drug (administered in Study 215ON201). In this circumstance, the SAE should be reported per Study 215ON201 protocol. To report initial or follow-up information on an SAE, fax a completed SAE form; refer to the Study Reference Guide for country-specific [redacted] fax number or email [redacted]

13.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF and reported as an SAE 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 [redacted]. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

13.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to study treatment (administered in Study 215ON201).

Biogen or designee will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

13.3.5. 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's Official Study Contact List for complete contact information.

13.4. Safety Responsibilities

13.4.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs and SAEs.
- Determine the relationship to study procedure(s) and to prior treatment with investigational drug (administered in Study 215ON201) and the severity of each event.
- Determine the onset and resolution dates of each event.
- Complete an SAE form for each SAE and fax it to [redacted] within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently until the event has resolved or become stable. Follow-up information must be reported to [redacted] within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable.

- Report SAEs to local ethics committees, as required by local law.

13.4.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor is responsible for reviewing with study site staff the definition of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

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

14. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

14.1. Efficacy

14.1.1. Analysis Population

Analysis of efficacy endpoints will be based on all enrolled subjects who complete the 1-day assessments.

14.1.2. General Methods of Analysis

Descriptive summary statistics will be presented for all study primary, secondary, and [redacted] endpoints collected.

Unless stated otherwise, summary statistics will be presented by original treatment groups and overall. For continuous endpoints, the summary statistics will generally include number of subjects enrolled, number of subjects evaluated, mean, standard deviation, median, and range (minimum, maximum). For categorical endpoints, the summary statistics will generally include number of subjects enrolled, number of subjects evaluated, and the percent of subjects in each category.

Statistical testing for efficacy endpoints will be made between the BIIB033 group and the placebo group. There will be no multiple comparison adjustments.

Unless stated otherwise, all statistical tests will be 2-sided with statistical significance level of 0.05.

14.1.2.1. Analysis of the Primary Endpoint

The primary analysis will be on the change in FF-VEP latency of the affected eye as compared to the baseline (measured prior to dosing in Study 215ON201) of the fellow eye at 2 years (+ up to 12 months) after the last study visit assessment (Week 32 or the projected Week 32 visit) in Study 215ON201. The ANCOVA model will be used to test the difference between the 2 original treatment groups from Study 215ON201, adjusting for the baseline of the unaffected fellow eye.

14.1.2.2. Analysis of the Secondary Endpoints

The secondary endpoints will include the time to diagnosis of CDMS; severity of disease evaluated by EDSS, SDMT, and MSFC (including T25FW, 9HPT, and PASAT); and brain MRI results. Number and percentage of subjects with diagnosis of CDMS will be summarized, and

descriptive statistics of time to diagnosis of CDMS will be presented. EDSS, SDMT, MSFC, and brain MRI outcomes will also be summarized using descriptive statistics.

[redacted]

14.2. Safety

14.2.1. Analysis Population

The safety population is defined as all enrolled subjects who complete the 1-day assessments.

14.2.2. Methods of Analysis

All AEs, clinical laboratory abnormalities, vital sign measurements, and physical examination findings will be evaluated for safety.

14.2.2.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. The incidence of clinical AEs will be summarized by severity and by relationship to study procedure(s) and to prior treatment with investigational drug (administered in Study 215ON201). The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class.

14.2.2.2. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The definitions of these clinically relevant abnormalities are shown in Table 2.

14.3. Interim Analyses

An interim analysis will be performed when approximately 50% of potential projected subjects have been enrolled into the study to provide information to assist the interpretation and design of ongoing clinical development of BIIB033 and other potential CNS remyelinating therapies. Statistical analyses listed in Section 14.1 will be performed on primary, secondary, and [redacted] endpoints at the interim analysis. Given that there is no intervention in this study, study stoppage does not apply. No stopping or continuation rules will be applied for the interim analysis.

14.4. Sample Size Considerations

The sample size is based on the number of subjects who participated in Study 215ON201 (approximately 82) rather than statistical considerations. The subjects eligible for this study must have participated in Study 215ON201.

15. ETHICAL REQUIREMENTS

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

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

15.1. Declaration of Helsinki

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

15.2. 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 all countries where subjects are enrolled.

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.

15.3. Subject Information and Consent

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

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

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

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

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

15.4. Subject Data Protection

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

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

15.5. Compensation for Injury

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

15.6. 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.

15.7. 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.

16. ADMINISTRATIVE PROCEDURES

16.1. Study Site Initiation

The Investigator must not enroll any subjects prior to completion of an on-site or remote study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

16.2. Quality Assurance

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

16.3. Monitoring of the Study

No site may initiate the 1-day assessments until Biogen or its designee representatives have concluded protocol-specific training and approved assessment technician(s).

Biogen or its designee representatives may conduct on-site visits at the study facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to subject (or associated) source files for the purpose of verifying entries made in the CRF and assist with their activities, if requested. Adequate space and time for monitoring visits should be made available by the Investigator or study staff. The site must complete the CRFs in a timely manner and on an ongoing basis to allow regular review by the study team.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

16.4. 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.

16.5. Publications

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

17. FURTHER REQUIREMENTS AND GENERAL INFORMATION

17.1. External Contract Organizations

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

17.1.1. Contract Research Organization

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

17.1.2. Electronic Data Capture

Subject information will be captured and managed by study sites on CRFs via an appropriate Web-based electronic remote data capture tool.

17.1.3. Central Facility for Other Assessments

A central facility has been selected by Biogen to be a central reader for [redacted], FF-VEP, and [redacted] for this study. A separate central facility has been selected by Biogen to read and interpret all MRI results for this study.

17.2. 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 15).

17.3. 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.

17.4. Retention of Study Data

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

17.5. Study Report Signatory

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

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

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19. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

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PROTOCOL NUMBER: 215ON203

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201

EUDRA CT NO: 2015-003618-26

DATE: 16 November 2015
Version 3.0
Final

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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

2. LIST OF ABBREVIATIONS

9HPT	9-Hole Peg Test
AE	adverse event
ANCOVA	analysis of covariance
AON	acute optic neuritis
CDMS	clinically definite multiple sclerosis
CI	confidence interval
CIS	clinically isolated syndrome
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
[redacted]	[redacted]
EDSS	Expanded Disability Status Scale
FITC-BIIB033	fluorescein isothiocyanate-conjugated BIIB033
FF-VEP	full-field visual evoked potential
[redacted]	[redacted]
GCP	Good Clinical Practice
Gd	gadolinium
IB	Investigator's Brochure
IP	Investigational product
HCVA	high-contrast visual acuity
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN-β	interferon-beta
IgG1	immunoglobulin G1
ITT	intent-to-treat
IV	intravenous
LCLA	low-contrast letter acuity
MAD	multiple-ascending dose
MFD	maximum feasible dose
[redacted]	[redacted]
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite
[redacted]	[redacted]
NEI-VFQ-25	25-item National Eye Institute Visual Function Questionnaire
[redacted]	[redacted]

PASAT	(3-Second) Paced Auditory Serial Addition Test
PK	pharmacokinetic(s)
RGCL	retinal ganglion cell layer
RNFL	retinal nerve fiber layer
[redacted]	[redacted]
RRMS	relapsing-remitting multiple sclerosis
SAD	single-ascending dose
SAE	serious adverse event
SC	subcutaneous
[redacted]	[redacted]
SDMT	Symbol-Digit Modalities Test
SPMS	secondary progressive multiple sclerosis
SUSAR	suspected unexpected serious adverse reaction
T25FW	Timed 25-Foot Walk

3. SYNOPSIS

Protocol Number:	215ON203
Protocol Title:	A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201
Version Number:	3.0
Study Indication:	Acute optic neuritis (AON)
Study Rationale:	BIIB033 (human anti-LINGO-1 monoclonal antibody) is an investigational product with the potential of enhancing remyelination and neuroaxonal protection. In Study 215ON201, treatment of patients with AON with BIIB033 displayed evidence of functional remyelination in the affected eye by demonstrating significant improvement in visual evoked potential latency over treatment with placebo. The electrophysiologic differences between the treatment and placebo groups were first observed at Week 12 during the dosing period and persisted throughout the subsequent monthly dosing visits. More interestingly, this trend continued for an additional 3 months through the Follow-Up Visit at Week 32 despite subjects completing the dosing period at Week 20. Study 215ON201 also showed that all subjects, regardless of assigned treatment, recovered clinically to a large extent regardless of treatment assignment or severity of injury to the retina or the optic nerve; however, not all subjects demonstrated complete functional recovery upon electrophysiologic examination. The rationale for the discrepancy between clinical recovery and electrophysiological improvement is unclear and requires further investigation. Given these data, the proposed follow-up study is necessary to assess the long-term electrophysiologic and clinical outcomes of this patient population with past randomized exposure to remyelinating therapy versus placebo and also to explore potential mechanism(s) by which patients recover

	from previous AON. This information will be critical in ongoing clinical development of remyelinating therapies so that they can be optimally evaluated and utilized for maximal benefit.
Phase of Development:	2
Study Objectives and Endpoints:	The primary objective of this study is to assess full-field visual evoked potential (FF-VEP) latency in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit. The primary endpoint that is related to this objective is the change in FF-VEP latency of the affected eye as compared to the baseline of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201. The secondary objective is to assess clinical progression and severity of central nervous system (CNS) demyelinating disease in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit. The endpoints that relate to this objective are as follows: • Evaluate incidence of clinically definite multiple sclerosis (CDMS) and time to diagnosis of CDMS. • Evaluate severity of CNS demyelinating disease with Expanded Disability Status Scale (EDSS), Symbol-Digit Modalities Test (SDMT), and multiple sclerosis functional composite (MSFC). The MSFC includes the following: – Timed 25-Foot Walk (T25FW) – 9-Hole Peg Test (9HPT) [dominant and nondominant hands] – (3-Second) Paced Auditory Serial Addition Test (PASAT) • Evaluate change in disease activity from baseline with brain magnetic resonance imaging (MRI)

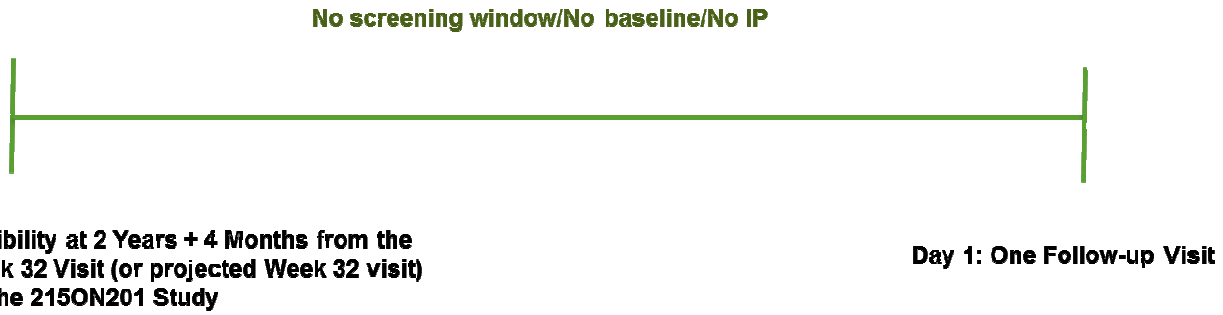
	with and without gadolinium (Gd). MRI analysis will include the following: – Number of Gd-enhanced lesions – Volume of T2 lesions [redacted]
Study Design:	This is a multicenter, follow-up study to determine the long-term electrophysiologic and clinical outcomes in subjects previously enrolled in Study 215ON201. One group is planned, with eligible subjects (previously enrolled in Study 215ON201) having been already administered at least 1 study treatment (BIIB033 100 mg/kg or placebo) by intravenous infusion once every 4 weeks for 20 weeks (a total of 6 doses). Dosing was completed 2 years (+ 4 months) prior to enrollment in this follow-up study. No additional study drug or placebo will be administered.
Study Location:	Approximately 33 sites globally are planned.
Number of Planned Subjects:	A maximum of 82 subjects will be eligible for enrollment (determined from the number of subjects who received at least 1 dose of BIIB033 100 mg/kg or placebo in Study 215ON201).
Study Population:	This study will be conducted in subjects who have participated in and received at least 1 dose of BIIB033 or placebo in Study 215ON201. Detailed criteria are described in Section 8.
Duration of Follow-up:	Eligible subjects will be enrolled at 2 years after their last study visit (Week 32) or projected Week 32 (+ 4 months) visit if the subject did not complete all visits in Study 215ON201. Subjects will perform 1 set of follow-up assessments at this timepoint.
Evaluations:	
Safety:	Assessments evaluating the safety profile will include physical examinations, vital sign measurements, and adverse

	events (AEs)/serious adverse events (SAEs). Any AE or SAE experienced by the subject after informed consent form sign-off through the end-of-study visit is to be recorded on the case report form or SAE form, respectively, regardless of the severity of the event or its relationship to study procedure(s) and/or to prior treatment with investigational drug (administered in Study 215ON201). Subjects will be followed for all SAEs until the event has resolved, stabilized, or returned to baseline status.
Statistical Analysis Methods:	The primary analysis will be on the change in FF-VEP latency of the affected eye as compared to the baseline (measured prior to dosing in Study 215ON201) of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201. The ANCOVA model will be used to test the difference between the 2 original treatment groups from Study 215ON201, adjusting for the baseline of the unaffected fellow eye. The secondary endpoints will include the time to diagnosis of CDMS; severity of disease evaluated by EDSS, SDMT, and MSFC (including T25FW, 9HPT, and PASAT); and brain MRI results. Number and percentage of subjects with diagnosis of CDMS will be summarized, and descriptive statistics of time to diagnosis of CDMS will be presented. EDSS, SDMT, MSFC, and brain MRI outcomes will also be summarized using descriptive statistics. [redacted]
Interim Analysis:	An interim analysis will be performed when approximately 50% of potentially projected available subjects have been enrolled into the study to provide information to assist the interpretation and design of ongoing clinical development of CNS remyelinating therapies.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 215ON203

4.1. Study Schematic

Figure 1: Study Design



IP = investigational product; MRI= magnetic resonance imaging.
Note: All assessments should be performed on the same day where possible or within a + 5-day window of the 1-day visit.

4.2. Schedule of Activities

Table 1: Schedule of Activities

Tests and Assessments[1]	**Day 1**[2]**:** **(2 Years + 4 Months After Week 32 Visit in Study 215ON201 or Projected Week 32 Visit if the Subject Did Not Complete All Visits)**
Informed Consent	X
Eligibility Criteria Check	X
Medical History[3]	X
Multiple Sclerosis Diagnosis	X
Multiple Sclerosis Signs and Symptoms	X
Concomitant Therapy and Procedures Recording	X
Vital Signs[4]	X
Physical Examination	X
Expanded Disability Status Scale[5]	X
Symbol-Digit Modalities Test	X
Multiple Sclerosis Functional Composite Including • Timed 25-Foot Walk • 9-Hole Peg Test (Dominant and Nondominant Hands) • (3-Second) Paced Auditory Serial Addition Test	X
[redacted]	

Tests and Assessments[1]	**Day 1**[2]**:** **(2 Years + 4 Months After Week 32 Visit in Study 215ON201 or Projected Week 32 Visit if the Subject Did Not Complete All Visits)**
[redacted]	
Full-Field Visual Evoked Potential[7]	X
[redacted]	
Adverse Event/Serious Adverse Event Recording[12]	X

[redacted]; MRI = magnetic resonance imaging.

[1] All assessments should be performed on the same day and in the order listed, when possible (or within a + 5-day window of the 1-day visit).

[2] Completion of the Day 1 visit assessments constitutes the end-of-study visit.

[3] Medical history will be taken from after last study visit in Study 215ON201.

[4] Vital signs include temperature, systolic and diastolic blood pressure, pulse rate, body weight, and respiratory rate (after sitting for at least 5 minutes).

[5] Expanded Disability Status Scale should be performed by a study certified rater. Where applicable, refer to study manual for instructions.

[redacted]

[7] Sites and technicians must be qualified and approved by the central reader to perform [redacted], full-field visual evoked potential, and [redacted].

[redacted]

[12] Adverse event/serious adverse event monitoring will be recorded after informed consent form sign-off through the end-of-study visit.

5. INTRODUCTION

BIIB033, a first-in-class human monoclonal antibody directed against LINGO-1, is a negative regulator of myelination and axonal growth. Antagonizing LINGO-1 with BIIB033 has the potential to enhance remyelination and neuroaxonal protection in the central nervous system (CNS).

LINGO-1 is a cell surface glycoprotein that is selectively expressed in the adult CNS in neurons and oligodendrocytes [Barrette 2007; Carim-Todd 2003; Llorens 2008; Mi 2004; Park 2005; Shao 2005]. It functions as a negative regulator of oligodendrocyte differentiation, myelination, and remyelination [Lee 2007; Mi 2005; Mi 2009; Mi 2008]. Axonal and neuronal expression of LINGO-1 increases after injury [Ji 2006; Mi 2004]. LINGO-1 expression prevents myelination of axons by oligodendrocytes.

Several nonclinical studies have demonstrated the potential for LINGO-1 antagonism to enhance CNS remyelination and neuroaxonal protection in animal models of toxic (cuprizone plus rapamycin) [Mi 2009], chemical (lysophosphatidylcholine), and inflammatory (myelin oligodendrocyte glycoprotein-experimental autoimmune encephalomyelitis) [Mi 2007] demyelination and of toxic (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) neuronal [Inoue 2007] and traumatic/hypertensive optic nerve [Fu 2008] and spinal cord [Ji 2008; Ji 2006] injury. The leading hypothesis for this clinical development program is that antagonism of LINGO-1 with BIIB033 will enhance remyelination and neuroaxonal protection in CNS demyelinating diseases such as multiple sclerosis (MS) and acute optic neuritis (AON), leading to CNS improvement with corresponding beneficial effects on neurological function and disability.

Additional details may be found in the BIIB033 Investigator's Brochure (IB).

5.1. Overview of Acute Optic Neuritis

The anterior visual pathway, particularly the optic nerve and its retinal nerve fiber layer (RNFL) and retinal ganglion cell layer (RGCL), is affected by AON and is a potential target for therapeutic compounds with properties to enhance remyelination and neuroaxonal protection. In a study of the long-term effects of AON in the context of MS, the RNFL was decreased to an average of 83 microns [Costello 2006; Talman 2010]. This corresponds to an average loss of ~20 microns or 20% of nerve fibers relative to unaffected eyes in patients with AON or to a loss of ~13 microns relative to eyes in patients with MS without history or presence of AON [Talman 2010]. Costello et al [Costello 2006] found that 74% of patients had 20% or greater thinning of the RNFL following AON. As also noted by Henderson et al [Henderson 2011 Aug], this RNFL thinning begins early (between 1 and 2 months after onset of AON), and nearly all of the eventual RNFL loss is complete by 6 months. This loss of RNFL is associated with a clinically important loss of visual function, as shown by a decrease of low-contrast letter acuity (LCLA) to an average of 21 letters out of 60 or a loss of 14 letters relative to unaffected MS eyes. There is also a permanent loss of visual motion perception in most patients affected by AON [Raz 2011].

Motion processing impairments in AON may be highly disruptive to the ability of patients to ambulate, drive, and navigate [Duffy 2011a; Duffy 2011b]. The permanent loss of visual function in AON is clinically important as reflected by a vision-related quality of life score of 84 on the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), which is 8 points lower than in unaffected patients [Balcer 2012]. This 8-point loss on the NEI-VFQ-25 is higher than the currently accepted 4-point threshold for clinically important changes in vision-related quality of life [Mowry 2009; Submacular Surgery Trials Research Group 2007].

5.2. Current Therapies for Acute Optic Neuritis

The only currently available treatment for AON is high-dose intravenous (IV) steroids (e.g., methylprednisolone) followed by an oral prednisone taper, which speeds up the recovery of symptoms (e.g., ocular pain) and high-contrast visual acuity (HCVA) primarily in the first 2 weeks after an attack, but has no long-term beneficial effects on the ultimate recovery of visual function [Beck 1992] nor is there evidence that it affects the degree of axonal loss or conduction velocity in the optic nerve pathway.

Despite treatment with high-dose steroids, over 60% of patients with AON are left with loss of visual function [Kupersmith 2007].

5.3. Overview of Multiple Sclerosis

MS is a chronic disabling neurological disease that affects an estimated 1 million people in North America and Western Europe. It is a disease of young adults, primarily women, with disease onset typically occurring between the ages of 20 and 40 years [Weinshenker 1989]. It is the most frequent cause of nontraumatic neurological disability affecting young adults in the Western world. Although the etiology is uncertain, evidence suggests that MS is, in part, an autoimmune disease directed against protein components of myelin. The diagnosis of clinically definite multiple sclerosis (CDMS) has traditionally been made on the basis of clinical criteria and requires that a patient experience at least 2 neurologic events consistent with demyelination, separated both in time and in location in the CNS [Poser 1983]. More recent diagnostic criteria have allowed for less than 2 neurologic attacks, when there is supportive laboratory evidence based on magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF) results [McDonald 2001]. The majority of patients with MS start out with a clinical course characterized by episodes or attacks (relapses) of neurologic dysfunction, which occur over many years. This phase of the disease is called relapsing-remitting multiple sclerosis (RRMS). Symptoms of such relapses include loss of vision or double vision, numbness or tingling sensation in the extremities, muscle weakness, slurred speech, difficulty with coordination, and bladder dysfunction. Patients having the first clinical attack are referred to as clinically isolated syndrome (CIS). The most common CIS types are AON, transverse myelitis, and brainstem attack. Patients with CIS with characteristic brain MRI lesions are considered to be having MS by the most recent diagnostic McDonald criteria [Polman 2011]. Patients with CIS without brain lesions are at low risk of developing MS. Early in the course of relapsing MS, the signs and symptoms tend to subside completely after each attack. Over time, there tends to be incomplete recovery from such attacks. The majority of patients with relapsing MS accumulate some

disability, and about half are unable to walk without assistance within 15 years of their initial diagnosis [Runmarker and Andersen 1993; Weinshenker 1989]. The majority of patients with RRMS eventually enter the secondary progressive phase of the disease (secondary progressive multiple sclerosis [SPMS]), characterized by steady worsening of disability independently of relapses. About 15% of the patients go into this progressive phase without prior development of a relapsing-remitting phase and are referred to as having a primary progressive MS.

5.4. Current Therapies for Multiple Sclerosis

Available therapies for the treatment of relapsing MS target the immunomodulation of inflammatory activity and include interferon-beta (IFN-β)1a, pegylated IFN-β1a, IFN-β1b, natalizumab, mitoxantrone, glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, and fingolimod. There is also 1 available symptomatic MS therapy to improve walking, prolonged-release fampridine, known as dalfampridine extended release in the United States.

5.5. Profile of Previous Experience with BIIB033

5.5.1. Nonclinical Experience

BIIB033 is a fully human aglycosylated immunoglobulin G1 (IgG1) monoclonal antibody that binds LINGO-1 with high affinity. As LINGO-1 is a cell surface glycoprotein selectively expressed in CNS oligodendrocytes and neurons that prevents myelination of axons by oligodendrocytes, a blockade of LINGO-1 may enhance remyelination and repair in CNS demyelinated lesions.

BIIB033 binds LINGO-1 with high affinity in humans, monkeys, rats, and mice; has high specificity for LINGO-1 and does not cross react with other LINGO family members; enhances differentiation of primary rat, monkey, and human oligodendrocytes in vitro; enhances axonal myelination in an in vitro rat dorsal root ganglion/oligodendrocyte precursor cell co-culture bioassay; has reduced Fcγ and complement effector functions compared to wild-type IgG1; and is efficacious in animal models using biochemical and functional readouts. These data suggest that BIIB033 will be an effective therapy to enhance remyelination in patients with MS.

An assessment of BIIB033 toxicology has been carried out in repeated-dose studies in rats and cynomolgus monkeys, as these species are considered pharmacologically relevant based on sequence homology with LINGO-1 and/or similarity in binding and in vitro functional activity with LINGO 1. Toxicology studies of up to 6 months in duration did not identify any adverse treatment-related effects or any effect on neurobehavioral assessments with weekly IV administrations of BIIB033 at up to a maximum feasible dose (MFD) of 316 mg/kg or 3-time-per week subcutaneous (SC) doses at up to 32 mg/kg. Effects on the CNS and respiratory system were transient, and none were considered adverse responses to BIIB033. In embryo-fetal toxicology studies in rats and rabbits, BIIB033 was shown to be not causing fetal abnormalities at maternal doses up to 316 mg/kg. Maternal toxicity and morbidity were noted in 1 rabbit given 316 mg/kg, but the relationship to BIIB033 treatment was unclear; no maternal toxicity was observed in rats at any dose.

Immunohistochemical analyses have identified target and nontarget antigen-specific cross-reactivity by fluorescein isothiocyanate-conjugated BIIB033 (FITC-BIIB033)-specific staining in a range of human, cynomolgus monkey, and rat tissues, including those of neural, epithelial, neuroendocrine, and connective tissue origins. Consistent BIIB033-specific immunostaining using 2 concentrations of FITC-BIIB033 was observed in the brain (primarily, the cerebral cortex) and spinal cord across all 3 species, and the pattern of FITC-BIIB033-specific staining was consistent with that of LINGO-1 protein localization, as previously observed in rodents. Additional non-neural tissues with inconsistent binding patterns across species were evaluated within the repeated-dose toxicology studies and were not identified as target organs of toxicity associated with BIIB033 administration up to an MFD dose over 6 months of treatment. The exposure-based safety margin for the highest dose planned for chronic dosing in the clinic (100 mg/kg/month) is projected to be 4- to 6-fold lower relative to exposures at the no-observed-adverse-effect level in toxicology species after 6 months of dosing.

Together, these data support ongoing evaluations of BIIB033 in Phase 2 studies.

See the IB for detailed information on nonclinical studies.

5.5.2. Clinical Experience

As of 07 May 2015, 72 healthy volunteers (54 BIIB033 and 18 placebo) have been dosed in a single-ascending-dose (SAD) clinical study (Study 215HV101), 47 subjects with MS (32 BIIB033 and 15 placebo) have been dosed in a multiple-ascending-dose (MAD) clinical study (Study 215MS101), 82 subjects with AON (41 BIIB033 and 41 placebo) have been dosed in a Phase 2 Study 215ON201, and 418 subjects with MS (treatment groups still blinded) have been dosed in the ongoing Phase 2 Study 215MS201.

Overall, BIIB033 has been well tolerated in clinical studies. In the completed Study 215HV101 (SAD), which evaluated the safety, tolerability, and pharmacokinetics (PK) of BIIB033 in healthy volunteers, doses ranging from 0.1 to 100 mg/kg BIIB033 were administered to a total of 54 healthy adult volunteers. There were no serious adverse events (SAEs) in the SAD study. Most adverse events (AEs) considered related to study treatment in the SAD study were mild, except for 3 moderate events (2 cases of headache and 1 case of gastroenteritis). The most common AEs with an incidence of ≥5% reported by subjects receiving BIIB033 were headache (10 subjects [19%]), upper respiratory tract infection (6 subjects [11%]), nasopharyngitis (4 subjects [7%]), and gastroenteritis (3 subjects [6%]). Overall, the frequency of AEs was similar between the BIIB033 and placebo groups.

In the completed Study 215MS101 (MAD), which evaluated the safety, tolerability, and PK of BIIB033 in subjects with RRMS or SPMS, multiple doses ranging from 0.3 to 100 mg/kg BIIB033 were administered to a total of 32 subjects. There were no SAEs in the MAD study. The frequency of AEs was similar in BIIB033-treated subjects compared with placebo-treated subjects. The most common AEs with an incidence of ≥5% reported by subjects receiving BIIB033 were headache and urinary tract infection (5 subjects [16%] each), upper respiratory

tract infection and MS relapse (3 subjects [9%] each), and postlumbar puncture headache (2 subjects [6%]).

The completed Phase 2 Study 215ON201 was designed to assess the efficacy, safety, tolerability, and PK of BIIB033 in subjects with their first episode of AON. In this study, the dose of 100 mg/kg BIIB033 was well tolerated, and the overall incidence of AEs was the same in the placebo and BIIB033 groups (34 subjects [83%] in each group). The most common AEs with an incidence of ≥10% reported by subjects receiving BIIB033 were nasopharyngitis (12 subjects [29%]), headache (11 subjects [27%]), fatigue (6 subjects [15%]), nausea (5 subjects [12%]), and paresthesia (4 subjects [10%]). There were 7 of 82 subjects (9%) who experienced SAEs, 5 subjects (12%) in the BIIB033 treatment group and 2 subjects (5%) in the placebo group. In the BIIB033 treatment group, 3 subjects had SAEs that were considered related to study treatment by the Investigator: 2 subjects with hypersensitivity reactions occurring during study treatment infusions and 1 subject with asymptomatic increased aspartate aminotransferase, increased alanine aminotransferase, and liver disorder. Two subjects in the BIIB033 treatment group experienced SAEs considered not related to study treatment. These included 1 subject with MS relapse and 1 subject with optic neuritis. All of the SAEs in the BIIB033 treatment group were reported as resolved. No anti-BIIB033 antibodies were seen in Study 215ON201, except for 1 subject who tested positive at predose baseline.

The reported events of hypersensitivity (serious and nonserious) in the clinical studies have occurred after the start of either the first or the second study treatment infusion in both Phase 1 and 2 studies. In all cases, the infusions were stopped, appropriate treatment was administered, and all events resolved.

The Phase 2 Study, 215MS201, was designed to assess the efficacy, safety, tolerability, and PK of BIIB033 in subjects with relapsing forms of MS when used concurrently with Avonex and is currently ongoing. In this study, the most common AEs with an incidence of ≥10% in the combined BIIB033 and placebo treatment groups are influenza like illness (175 subjects [42%]), MS relapse (123 subjects [29%]), headache (68 subjects [16%]), upper respiratory tract infection (51 subjects [12%]), urinary tract infection (46 subjects [11%]), pyrexia (44 subjects [11%]), and nasopharyngitis (40 subjects [10%]). Fifty of 418 subjects enrolled (12%) reported SAEs as of 07 May 2015. SAEs that were reported in more than 1 subject included MS relapse (27 subjects [6%]), urinary tract infection (3 subjects [<1%]), and hypersensitivity (4 subjects [<1%]). As this study is still ongoing, the treatment codes are blinded, and it is not known if the events occurred in subjects treated with BIIB033 or placebo.

BIIB033 PK following a single dose (IV and SC) up to 100 mg/kg in healthy volunteers and 2 repeated IV doses up to 100 mg/kg in subjects with MS was characterized in the SAD and MAD studies, respectively. BIIB033 PK appears to be similar between healthy volunteers and subjects with MS. In general, BIIB033 PK was linear with small volume of distribution at steady state, minimal target-mediated clearance, and an elimination half-life of approximately 2 to 3 weeks. As expected, the CSF/serum concentration ratio for BIIB033 in humans is estimated to be approximately 0.1%. In the Phase 2 Study 215ON201, the preliminary PK results suggest that

the predicted BIIB033 pharmacological exposure at 100 mg/kg was achieved in subjects with AON, and BIIB033 PK appears to be similar to healthy adults and subjects with MS.

Please refer to the BIIB033 IB for additional details and results on clinical studies.

5.6. Study Rationale

A biological effect of BIIB033 was shown in Study 215ON201 in subjects with AON. In this study, subjects received 6 doses of 100 mg/kg BIIB033 or placebo administered via IV infusion every 4 weeks up to Week 20, with Follow-Up Visits at Weeks 24 and 32. Efficacy results showed an improvement in mean change in full-field visual evoked potential (FF-VEP) latency values of the affected eye from the baseline of the fellow eye at Week 24 in the BIIB033 group compared with placebo in the intent-to-treat population (-3.48 [95% confidence interval (CI): -10.61, 3.65] msec, analysis of covariance [ANCOVA]). The treatment effect was more pronounced in the per-protocol population (-7.55 [95% CI: -15.12, 0.01] msec, ANCOVA). The electrophysiologic differences between the treatment and placebo groups, first observed at Week 12 during the dosing period, persisted throughout the subsequent monthly dosing visits.

The change in FF-VEP latency in the affected eye versus the baseline of the unaffected fellow eye by mixed model for repeated measures (MMRM) showed a greater treatment effect at Week 32 than at Week 24 for both the intent-to-treat (ITT) and per-protocol populations, despite subjects completing the dosing period at Week 20. In the ITT population, an improvement of -6.06 msec over placebo was seen in the BIIB033 group at Week 32 by MMRM ($p = 0.0711$). A significant improvement of -9.13 msec over placebo was seen in the BIIB033 group at Week 32 in the per-protocol population by MMRM ($p = 0.0112$).

Study 215ON201 also showed that all subjects, regardless of assigned treatment, recovered clinically to a large extend regardless of treatment assignment or severity of injury to the retina or the optic nerve; however, not all subjects demonstrated complete functional recovery upon electrophysiologic examination. The rationale for the discrepancy between clinical recovery and electrophysiological improvement is unclear and requires further investigation.

Given these data, the proposed follow-up study is necessary to assess the long-term electrophysiologic and clinical outcomes of this patient population with past randomized exposure to remyelinating therapy versus placebo, but also to explore potential mechanism(s) by which patients recover from previous AON. This information will be critical in the ongoing clinical development of remyelinating therapies so that they can be optimally evaluated and utilized for maximal benefit.

Please refer to the BIIB033 IB for additional details and results on Study 215ON201.

5.7. Rationale for Dosing Regimen

No study drug dosing is planned for this follow-up study.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to assess FF-VEP latency in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit.

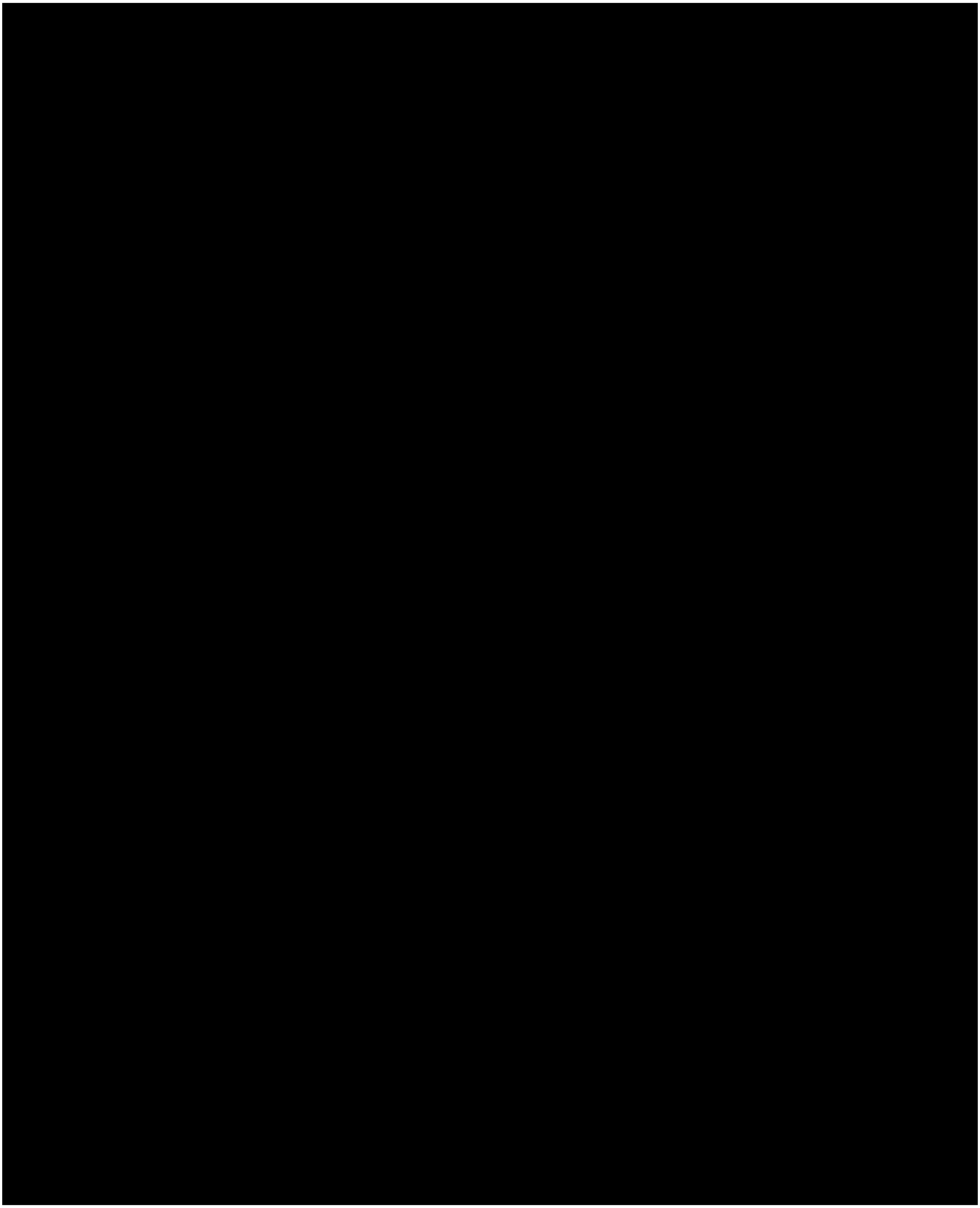
The primary endpoint that is related to this objective is the change in FF-VEP latency of the affected eye as compared to the baseline of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201.

6.2. Secondary Objectives and Endpoints

The secondary objective is to assess clinical progression and severity of CNS demyelinating disease in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit.

The endpoints that relate to this objective are as follows:

- Evaluate incidence of CDMS and time to diagnosis of CDMS.
- Evaluate severity of CNS demyelinating disease with Expanded Disability Status Scale (EDSS), Symbol-Digit Modalities Test (SDMT), and multiple sclerosis functional composite (MSFC). MSFC includes the following:
  - Timed 25-Foot Walk (T25FW)
  - 9-Hole Peg Test (9HPT) [dominant and nondominant hands]
  - (3-Second) Paced Auditory Serial Addition Test (PASAT)
- Evaluate change in disease activity from baseline with brain MRI with and without gadolinium (Gd). MRI analysis will include the following:
  - Number of Gd-enhanced lesions
  - Volume of T2 lesions



7. STUDY DESIGN

7.1. Study Overview

This multicenter, follow-up study will determine the long-term electrophysiologic and clinical outcomes in subjects previously enrolled in Study 215ON201.

One group is planned, with eligible subjects (previously enrolled in Study 215ON201) having been already administered at least 1 study treatment (BIIB033 100 mg/kg or placebo) by IV infusion once every 4 weeks for 20 weeks (a total of 6 doses). Dosing was completed 2 years (+ 4 months) prior to enrollment in this follow-up study. A maximum of 82 subjects (determined from the number of subjects who received at least 1 dose of BIIB033 or placebo in Study 215ON201) will be included in this study. There is no formal sample size calculation. The number of subjects eligible for this study is determined by the number of subjects who participated in Study 215ON201.

See Figure 1 for a schematic of the study design.

7.2. Overall Study Duration

The study period will consist of an approximately 1-day visit (with a + 5-day window of the 1-day visit) that is dependent on the scanner capabilities and equipment availability at each clinical site.

7.2.1. Screening

Subject eligibility for the study will be determined by the date of 2 years (+ 4 months) after the last study visit (Week 32) or projected Week 32 visit, if the subject did not complete all visits in Study 215ON201. There is no screening visit in this study.

7.2.2. Treatment

No study drug dosing is planned for this study.

7.2.3. Visit Schedule

Each subject will have approximately 1 scheduled study visit (with a + 5-day window of the 1-day visit) that is dependent on the scanner capabilities and equipment availability at each clinical site.

7.3. Study Stopping Rules

Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

7.4. End of Study

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

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of Day 1 visit or at the timepoint specified in the individual eligibility criterion listed:

1. Must have participated in Study 215ON201 and received at least 1 dose of BIIB033 or placebo, as per protocol, within 2 years (+ 4 months) from Day 1 of this study (2 years from Week 32 or projected Week 32 visit, if the subject did not complete all visits in Study 215ON201).

2. 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.

8.2. Exclusion Criteria

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

1. Not previously enrolled in Study 215ON201.

2. Inability to comply with study requirements.

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

4. Subjects with recent kidney function, such as serum creatinine above upper limit of normal range, will not be allowed to receive administration of Gd but will otherwise be allowed to participate in the study, including MRI assessments not requiring the use of Gd.

5. Female subjects must have had a recent pregnancy test and must not be breastfeeding prior to MRI assessments with Gd.

9. ENROLLMENT AND REGISTRATION

9.1. Enrollment

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any study-related tests are performed (see Section 15.3). When a subject signs the informed consent form (ICF), that subject is considered to be enrolled 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 enrolment log.

9.2. Registration of Subjects

Subjects will be registered at 2 years (+ 4 months) after their last study visit (Week 32) or projected Week 32 visit, if the subjects did not complete all visits in Study 215ON201, and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2.

Refer to the Study Reference Guide for details on registration.

9.3. Blinding Procedures

This is a follow-up study with no investigational product, therefore blinding is not applicable. As much as possible, the treatment disclosure for Study 215ON201 should not be shared with sites or patients until the end of this study to reduce the risk of bias on the follow on assessments based on knowledge of treatment.

10. WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Sponsor or Investigator for medical reasons or for noncompliance.

The reason for the subject's withdrawal from the study must be recorded in the subject's case report form (CRF).

11. FOLLOW-UP ASSESSMENTS

See Section 4 for the timing of all assessments.

11.1. One-Day Visit Assessments

This study will assess the electrophysiological function of the visual pathway using FF-VEP. The various electrophysiologic and imaging measurements will be made to assess feasibility of being utilized as potential clinical endpoints sensitive to remyelination therapy in multicenter clinical studies (Table 1). Clinical progression and severity of disease will be assessed by the following:

- Medical history, including date of diagnosis of CDMS
- MS diagnosis
- MS signs and symptoms
- Concomitant therapy and procedures recording
- Vital signs
- Physical examination
- EDSS
- SDMT
- MSFC (including T25FW, 9HPT, and PASAT)
- [redacted]
- [redacted]
- FF-VEP
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- AE and SAE recording

12. SAFETY ASSESSMENTS

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

12.1. Safety Assessments

The following safety assessments will be performed:

- Physical examinations
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, body weight, and respiratory rate
- AE and SAE recording

12.2. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The definitions of these clinically relevant abnormalities are shown in Table 2.

Table 2: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C
Pulse	>100 bpm <40 bpm
Systolic Blood Pressure	>160 mmHg <90 mmHg
Diastolic Blood Pressure	>100 mmHg <45 mmHg

bpm = beats per minute.

13. SAFETY DEFINITIONS, CLASSIFICATIONS, 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 must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

13.1. Definition

13.1.1. Adverse Event

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

13.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.

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

13.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
  - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 13.1.2 is met.

13.2. Safety Classifications

13.2.1. 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 13.1.2.
- The relationship of the event to the study procedure(s) and to prior treatment with investigational drug (administered in Study 215ON201) as defined in Section 13.2.2.
- The severity of the event as defined in Section 13.2.3.

13.2.2. Relationship of Events to Study Procedure(s) and Prior Treatment With Investigational Drug

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study procedure(s) and to prior treatment with investigational drug:

Relationship of Event to Study Procedure(s) and to Prior Treatment With Investigational Drug (Administered in Study 215ON201)	
Not related	An AE will be considered "not related" to the study procedure(s) and/or investigational drug (administered in Study 215ON201) if there is not a reasonable possibility that the event has been caused by the study procedure(s) and/or investigational drug. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between study procedure(s) and/or investigational drug and the event, the presence of a biologically implausible relationship between the study procedure(s) and/or investigational drug and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the study procedure(s) and/or investigational drug (administered in Study 215ON201) if there is a reasonable possibility that the event may have been caused by the study procedure(s) and/or investigational drug. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between study procedure(s) and/or investigational drug and the event, a known response pattern of the study procedure(s) and/or investigational drug, a biologically plausible relationship between the study procedure(s) and/or investigational drug and the AE, or a lack of an alternative explanation for the AE.

13.2.3. Severity of Events

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

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of study procedure(s); treatment for symptoms may be given and/or subject hospitalized.

13.2.4. Expectedness of Events

Expectedness of all AEs due to previous exposure to BIIB033 will be determined by Biogen according to the IB.

13.3. Monitoring and Recording Events

13.3.1. Adverse Events

Any AE experienced by the subject after ICF sign-off through the end-of-study visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study procedure(s) and/or to prior treatment with the investigational drug (administered in Study 215ON201).

13.3.2. Serious Adverse Events

Any SAE experienced by a subject after ICF sign-off through the end-of-study visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study procedure(s) and/or to prior treatment with the investigational drug (administered in Study 215ON201). SAEs must be reported to [redacted] within 24 hours as described in Section 13.3.3. Follow-up information regarding an SAE also must be reported within 24 hours.

Subjects will be followed for all SAEs until the event has resolved, stabilized, or returned to baseline status.

13.3.3. 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 [redacted] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs
Any SAE that occurs after ICF sign-off through the end-of-study visit must be reported to [redacted] within 24 hours of the study site staff becoming aware of the event. After the end-of-study visit, the SAE should only be reported if the Investigator considers it related to investigational drug (administered in Study 215ON201). In this circumstance, the SAE should be reported per Study 215ON201 protocol. To report initial or follow-up information on an SAE, fax a completed SAE form; refer to the Study Reference Guide for country-specific [redacted] fax number or email [redacted].

13.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF and reported as an SAE 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 [redacted]. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

13.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to study treatment (administered in Study 215ON201).

Biogen or designee will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

13.3.5. 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's Official Study Contact List for complete contact information.

13.4. Safety Responsibilities

13.4.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs and SAEs.
- Determine the relationship to study procedure(s) and to prior treatment with investigational drug (administered in Study 215ON201) and the severity of each event.
- Determine the onset and resolution dates of each event.
- Complete an SAE form for each SAE and fax it to [redacted] within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently until the event has resolved or become stable. Follow-up information must be reported to [redacted] within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable.

- Report SAEs to local ethics committees, as required by local law.

13.4.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor is responsible for reviewing with study site staff the definition of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

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

14. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

14.1. Efficacy

14.1.1. Analysis Population

Analysis of efficacy endpoints will be based on all enrolled subjects who complete the 1-day assessments.

14.1.2. General Methods of Analysis

Unless stated otherwise, summary statistics will be presented by original treatment groups and overall. For continuous endpoints, the summary statistics will generally include number of subjects enrolled, number of subjects evaluated, mean, standard deviation, median, and range. For categorical endpoints, the summary statistics will generally include number of subjects enrolled, number of subjects evaluated, and the percent of subjects in each category.

14.1.2.1. Analysis of the Primary Endpoint

The primary analysis will be on the change in FF-VEP latency of the affected eye as compared to the baseline (measured prior to dosing in Study 215ON201) of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201. The ANCOVA model will be used to test the difference between the 2 original treatment groups from Study 215ON201, adjusting for the baseline of the unaffected fellow eye.

14.1.2.2. Analysis of the Secondary Endpoints

The secondary endpoints will include the time to diagnosis of CDMS; severity of disease evaluated by EDSS, SDMT, and MSFC (including T25FW, 9HPT, and PASAT); and brain MRI results. Number and percentage of subjects with diagnosis of CDMS will be summarized, and descriptive statistics of time to diagnosis of CDMS will be presented. EDSS, SDMT, MSFC, and brain MRI outcomes will also be summarized using descriptive statistics.

[redacted]

14.2. Safety

14.2.1. Analysis Population

The safety population is defined as all enrolled subjects who complete the 1-day assessments.

14.2.2. Methods of Analysis

All AEs, clinical laboratory abnormalities, vital sign measurements, and physical examination findings will be evaluated for safety.

14.2.2.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. The incidence of clinical AEs will be summarized by severity and by relationship to study procedure(s) and to prior treatment with investigational drug (administered in Study 215ON201). The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class.

14.2.2.2. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The definitions of these clinically relevant abnormalities are shown in Table 2.

14.3. Interim Analyses

An interim analysis will be performed when approximately 50% of potentially projected available subjects have been enrolled into the study to provide information to assist the interpretation and design of ongoing clinical development of CNS remyelinating therapies. Statistical analyses listed in Section 14.1 will be performed on primary, secondary, and [redacted] endpoints at the interim analysis.

14.4. Sample Size Considerations

The sample size is based on the number of subjects who participated in Study 215ON201 (approximately 82) rather than statistical considerations. The subjects eligible for this study must have participated in Study 215ON201.

15. ETHICAL REQUIREMENTS

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

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

15.1. Declaration of Helsinki

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

15.2. 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 all countries where subjects are enrolled.

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.

15.3. Subject Information and Consent

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

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

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

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

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

15.4. Subject Data Protection

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

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

15.5. Compensation for Injury

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

15.6. 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.

15.7. 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.

16. ADMINISTRATIVE PROCEDURES

16.1. Study Site Initiation

The Investigator must not enroll any subjects prior to completion of an on-site or remote study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

16.2. Quality Assurance

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

16.3. Monitoring of the Study

No site may initiate the 1-day assessments until Biogen or its designee representatives have concluded protocol-specific training and approved assessment technician(s).

Biogen or its designee representatives may conduct on-site visits at the study facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to subject (or associated) source files for the purpose of verifying entries made in the CRF and assist with their activities, if requested. Adequate space and time for monitoring visits should be made available by the Investigator or study staff. The site must complete the CRFs in a timely manner and on an ongoing basis to allow regular review by the study team.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

16.4. 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.

16.5. Publications

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

17. FURTHER REQUIREMENTS AND GENERAL INFORMATION

17.1. External Contract Organizations

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

17.1.1. Contract Research Organization

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

17.1.2. Electronic Data Capture

Subject information will be captured and managed by study sites on CRFs via an appropriate Web-based electronic remote data capture tool.

17.1.3. Central Facility for Other Assessments

A central facility has been selected by Biogen to be a central reader for SD-OCT, FF-VEP, and mfVEP for this study. A separate central facility has been selected by Biogen to read and interpret all MRI results for this study.

17.2. 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 15).

17.3. 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.

17.4. Retention of Study Data

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

17.5. Study Report Signatory

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

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

18. REFERENCES

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19. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

Signature Page

Document Name: 215ON203 Protocol V3 Final 16Nov15

Document Title: A Multicenter, Follow-Up Study to Assess Long Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201

Signed by	Role	Date / Time (UTC)
[redacted]	Signing as Approver	16-Nov-2015 19:57:07

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PROTOCOL NUMBER: 215ON203

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201

EUDRA CT NO: 2015-003618-26

DATE: 01 September 2015
Version 2.0
Final

SPONSOR SIGNATURE

Protocol 215ON203 was approved by:

[redacted], MD [redacted]

Biogen MA Inc.

8 September 2015

Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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

2. LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
AON	acute optic neuritis
CDMS	clinically definite multiple sclerosis
CI	confidence interval
CIS	clinically isolated syndrome
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
[redacted]	[redacted]
EDSS	Expanded Disability Status Scale
FITC-BIIB033	fluorescein isothiocyanate-conjugated BIIB033
FF-VEP	full-field visual evoked potential
[redacted]	[redacted]
GCP	Good Clinical Practice
Gd	gadolinium
IB	Investigator's Brochure
IP	Investigational product
HCVA	high-contrast visual acuity
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN-β	interferon-beta
IgG1	immunoglobulin G1
ITT	intent-to-treat
IV	intravenous
LCLA	low-contrast letter acuity
MAD	multiple-ascending dose
MFD	maximum feasible dose
[redacted]	[redacted]
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite
[redacted]	[redacted]
[redacted]	[redacted]
NEI-VFQ-25	25-item National Eye Institute Visual Function Questionnaire
[redacted]	[redacted]
PK	pharmacokinetic(s)

RGCL	retinal ganglion cell layer
RNFL	retinal nerve fiber layer
[redacted]	[redacted]
RRMS	relapsing-remitting multiple sclerosis
SAD	single-ascending dose
SAE	serious adverse event
SC	subcutaneous
[redacted]	[redacted]
SPMS	secondary progressive multiple sclerosis

3. SYNOPSIS

Protocol Number:	215ON203
Protocol Title:	A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201
Version Number:	2.0
Study Indication:	Acute optic neuritis (AON)
Study Rationale:	BIIB033 (human anti-LINGO-1 monoclonal antibody) is an investigational product with the potential of enhancing remyelination and neuroaxonal protection. In Study 215ON201, treatment of patients with AON with BIIB033 displayed evidence of functional remyelination in the affected eye by demonstrating significant improvement in visual evoked potential latency over treatment with placebo. The electrophysiologic differences between the treatment and placebo groups were first observed at Week 12 during the dosing period and persisted throughout the subsequent monthly dosing visits. More interestingly, this trend continued for an additional 3 months through the Follow-Up Visit at Week 32 despite subjects completing the dosing period at Week 20. Study 215ON201 also showed that all subjects, regardless of assigned treatment, recovered clinically to a large extent regardless of treatment assignment or severity of injury to the retina or the optic nerve; however, not all subjects demonstrated complete functional recovery upon electrophysiologic examination. The rationale for the discrepancy between clinical recovery and electrophysiological improvement is unclear and requires further investigation. Given these data, the proposed follow-up study is necessary to assess the long-term electrophysiologic and clinical outcomes of this patient population with past randomized exposure to remyelinating therapy versus placebo and also to explore potential mechanism(s) by which patients recover

	from previous AON. This information will be critical in ongoing clinical development of remyelinating therapies so that they can be optimally evaluated and utilized for maximal benefit.
Phase of Development:	2
Study Objectives and Endpoints:	The primary objective of this study is to assess full-field visual evoked potential (FF-VEP) latency in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit. The primary endpoint that is related to this objective is the change in FF-VEP latency of the affected eye as compared to the baseline of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201. The secondary objective is to assess clinical progression and severity of central nervous system (CNS) demyelinating disease in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit. The endpoints that relate to this objective are as follows: • Evaluate incidence of clinically definite multiple sclerosis (CDMS) and time to diagnosis of CDMS. • Evaluate severity of CNS demyelinating disease with Expanded Disability Status Scale (EDSS) and multiple sclerosis functional composite (MSFC). • Evaluate change in disease activity from baseline with brain magnetic resonance imaging (MRI) with and without gadolinium (Gd). MRI analysis will include the following: – Number of Gd-enhanced lesions – Volume of T2 lesions [redacted]

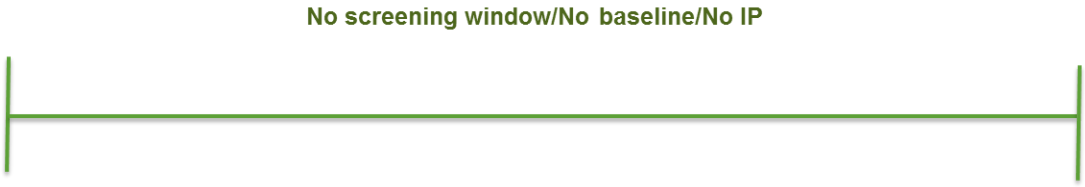
Study Design:	This is a multicenter, follow-up study to determine the long-term electrophysiologic and clinical outcomes in subjects previously enrolled in Study 215ON201. One group is planned, with eligible subjects (previously enrolled in Study 215ON201) having been already administered at least 1 study treatment (BIIB033 100 mg/kg or placebo) by intravenous infusion once every 4 weeks for 20 weeks (a total of 6 doses). Dosing was completed 2 years (+ 4 months) prior to enrollment in this follow-up study. No additional drug or placebo will be administered.
Study Location:	Approximately 33 sites globally are planned.
Number of Planned Subjects:	A maximum of 82 subjects will be eligible for enrollment (determined from the number of subjects who received at least 1 dose of BIIB033 100 mg/kg or placebo in Study 215ON201).
Study Population:	This study will be conducted in subjects who have participated in and received at least 1 dose of BIIB033 or placebo in Study 215ON201. Detailed criteria are described in Section 8.
Duration of Follow-up:	Eligible subjects will be enrolled at 2 years after their last study visit (Week 32) or projected Week 32 (+ 4 months) visit if the subject did not complete all visits in Study 215ON201. Subjects will perform 1 set of follow-up assessments at this timepoint.
Evaluations:	
Safety:	Assessments evaluating the safety profile related to study procedure(s) will include physical examinations, vital sign measurements, and serious adverse events (SAEs). Any SAE experienced by a subject post informed consent form sign-off through end-of-study visit and considered by the Investigator to be related to study procedure(s) is to be recorded on an SAE form, regardless of the severity of the event. Information on SAEs related to study procedure(s) must be reported to [redacted] within 24 hours.

	Subjects will be followed for all SAEs until the event has resolved, stabilized, or returned to baseline status.
Statistical Analysis Methods:	The primary analysis will be on the change in FF-VEP latency of the affected eye as compared to the baseline (measured prior to dosing in Study 215201) of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201. The ANCOVA model will be used to test the difference between the 2 original treatment groups from Study 215ON201, adjusting for the baseline of the unaffected fellow eye. The secondary endpoints will include the time to diagnosis of CDMS, severity of disease evaluated by EDSS and MSFC, and brain MRI results. Number and percentage of subjects with diagnosis of CDMS will be summarized, and descriptive statistics of time to diagnosis of CDMS will be presented. EDSS, MSFC, and brain MRI outcomes will also be summarized using descriptive statistics. [redacted]
Interim Analysis:	An interim analysis will be performed when approximately 50% of potentially projected available subjects have been enrolled into the study to provide information to assist the interpretation and design of ongoing clinical development of CNS remyelinating therapies.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 215ON203

4.1. Study Schematic

Figure 1: Study Design



IP = investigational product; MRI= magnetic resonance imaging.
Note: All assessments should be performed on the same day where possible or within a + 5 day window of the 1-day visit.

4.2. Schedule of Activities

Table 1: Schedule of Activities

Tests and Assessments[1]	Day 1: (2 Years + 4 Months After Week 32 Visit in Study 215ON201 or Projected Week 32 Visit if the Subject Did Not Complete All Visits)
Informed Consent	X
Eligibility Criteria Check	X
Medical History[2]	X
Multiple Sclerosis Diagnosis	X
Multiple Sclerosis Signs and Symptoms	X
Concomitant Therapy and Procedures Recording	X
Vital Signs[3]	X
Physical Examination	X
Expanded Disability Status Scale[4]	X
Multiple Sclerosis Functional Composite	X
[redacted]	
Full-Field Visual Evoked Potential[6]	X
[redacted]	

Tests and Assessments[1]	Day 1: (2 Years + 4 Months After Week 32 Visit in Study 215ON201 or Projected Week 32 Visit if the Subject Did Not Complete All Visits)
[redacted]	
Serious Adverse Events Related to Study Procedure(s) Reporting[11]	X

[redacted]; MRI = magnetic resonance imaging.

[1] All assessments should be performed on the same day and in the order listed, when possible (or within a + 5 day window of the 1-day visit).

[2] Medical history will be taken from after last study visit in Study 215ON201.

[3] Vital signs include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate (after sitting down for at least 5 minutes).

[4] Expanded Disability Status Scale should be performed by a study certified rater. Where applicable, refer to study manual for instructions.

[redacted]

[6] Sites and technicians must be qualified and approved by the central reader to perform [redacted], full-field visual evoked potential, and [redacted].

[redacted]

[11] Serious adverse events monitoring for events related to study procedure(s) will be reported post informed consent form sign-off through end-of-study visit.

5. INTRODUCTION

BIIB033, a first-in-class human monoclonal antibody directed against LINGO-1, is a negative regulator of myelination and axonal growth. Antagonizing LINGO-1 with BIIB033 has the potential to enhance remyelination and neuroaxonal protection in the central nervous system (CNS).

LINGO-1 is a cell surface glycoprotein that is selectively expressed in the adult CNS in neurons and oligodendrocytes [Barrette 2007; Carim-Todd 2003; Llorens 2008; Mi 2004; Park 2005; Shao 2005]. It functions as a negative regulator of oligodendrocyte differentiation, myelination, and remyelination [Lee 2007; Mi 2005; Mi 2009; Mi 2008]. Axonal and neuronal expression of LINGO-1 increases after injury [Ji 2006; Mi 2004]. LINGO-1 expression prevents myelination of axons by oligodendrocytes.

Several nonclinical studies have demonstrated the potential for LINGO-1 antagonism to enhance CNS remyelination and neuroaxonal protection in animal models of toxic (cuprizone plus rapamycin) [Mi 2009], chemical (lysophosphatidylcholine), and inflammatory (myelin oligodendrocyte glycoprotein-experimental autoimmune encephalomyelitis) [Mi 2007] demyelination and of toxic (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) neuronal [Inoue 2007] and traumatic/hypertensive optic nerve [Fu 2008] and spinal cord [Ji 2008; Ji 2006] injury. The leading hypothesis for this clinical development program is that antagonism of LINGO-1 with BIIB033 will enhance remyelination and neuroaxonal protection in CNS demyelinating diseases such as multiple sclerosis (MS) and acute optic neuritis (AON), leading to CNS improvement with corresponding beneficial effects on neurological function and disability.

Additional details may be found in the BIIB033 Investigator's Brochure (IB).

5.1. Overview of Acute Optic Neuritis

The anterior visual pathway, particularly the optic nerve and its retinal nerve fiber layer (RNFL) and retinal ganglion cell layer (RGCL), is affected by AON and is a potential target for therapeutic compounds with properties to enhance remyelination and neuroaxonal protection. In a study of the long-term effects of AON in the context of MS, the RNFL was decreased to an average of 83 microns [Costello 2006; Talman 2010]. This corresponds to an average loss of ~20 microns or 20% of nerve fibers relative to unaffected eyes in patients with AON or to a loss of ~13 microns relative to eyes in patients with MS without history or presence of AON [Talman 2010]. Costello et al [Costello 2006] found that 74% of patients had 20% or greater thinning of the RNFL following AON. As also noted by Henderson et al [Henderson 2011 Aug], this RNFL thinning begins early (between 1 and 2 months after onset of AON), and nearly all of the eventual RNFL loss is complete by 6 months. This loss of RNFL is associated with a clinically important loss of visual function, as shown by a decrease of low-contrast letter acuity (LCLA) to an average of 21 letters out of 60 or a loss of 14 letters relative to unaffected MS eyes. There is also a permanent loss of visual motion perception in most patients affected by AON [Raz 2011].

Motion processing impairments in AON may be highly disruptive to the ability of patients to ambulate, drive, and navigate [Duffy 2011a; Duffy 2011b]. The permanent loss of visual function in AON is clinically important as reflected by a vision-related quality of life score of 84 on the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), which is 8 points lower than in unaffected patients [Balcer 2012]. This 8-point loss on the NEI-VFQ-25 is higher than the currently accepted 4-point threshold for clinically important changes in vision-related quality of life [Mowry 2009; Submacular Surgery Trials Research Group 2007].

5.2. Current Therapies for Acute Optic Neuritis

The only currently available treatment for AON is high-dose intravenous (IV) steroids (e.g., methylprednisolone) followed by an oral prednisone taper, which speeds up the recovery of symptoms (e.g., ocular pain) and high-contrast visual acuity (HCVA) primarily in the first 2 weeks after an attack, but has no long-term beneficial effects on the ultimate recovery of visual function [Beck 1992] nor is there evidence that it affects the degree of axonal loss or conduction velocity in the optic nerve pathway.

Despite treatment with high-dose steroids, over 60% of patients with AON are left with loss of visual function [Kupersmith 2007].

5.3. Overview of Multiple Sclerosis

MS is a chronic disabling neurological disease that affects an estimated 1 million people in North America and Western Europe. It is a disease of young adults, primarily women, with disease onset typically occurring between the ages of 20 and 40 years [Weinshenker 1989]. It is the most frequent cause of nontraumatic neurological disability affecting young adults in the Western world. Although the etiology is uncertain, evidence suggests that MS is, in part, an autoimmune disease directed against protein components of myelin. The diagnosis of clinically definite multiple sclerosis (CDMS) has traditionally been made on the basis of clinical criteria and requires that a patient experience at least 2 neurologic events consistent with demyelination, separated both in time and in location in the CNS [Poser 1983]. More recent diagnostic criteria have allowed for less than 2 neurologic attacks, when there is supportive laboratory evidence based on magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF) results [McDonald 2001]. The majority of patients with MS start out with a clinical course characterized by episodes or attacks (relapses) of neurologic dysfunction, which occur over many years. This phase of the disease is called relapsing-remitting multiple sclerosis (RRMS). Symptoms of such relapses include loss of vision or double vision, numbness or tingling sensation in the extremities, muscle weakness, slurred speech, difficulty with coordination, and bladder dysfunction. Patients having the first clinical attack are referred to as clinically isolated syndrome (CIS). The most common CIS types are AON, transverse myelitis, and brainstem attack. Patients with CIS with characteristic brain MRI lesions are considered to be having MS by the most recent diagnostic McDonald criteria [Polman 2011]. Patients with CIS without brain lesions are at low risk of developing MS. Early in the course of relapsing MS, the signs and symptoms tend to subside completely after each attack. Over time, there tends to be incomplete recovery from such attacks. The majority of patients with relapsing MS accumulate some

disability, and about half are unable to walk without assistance within 15 years of their initial diagnosis [Runmarker and Andersen 1993; Weinshenker 1989]. The majority of patients with RRMS eventually enter the secondary progressive phase of the disease (secondary progressive multiple sclerosis [SPMS]), characterized by steady worsening of disability independently of relapses. About 15% of the patients go into this progressive phase without prior development of a relapsing-remitting phase and are referred to as having a primary progressive MS.

5.4. Current Therapies for Multiple Sclerosis

Available therapies for the treatment of relapsing MS target the immunomodulation of inflammatory activity and include interferon-beta (IFN-β)1a, pegylated IFN-β1a, IFN-β1b, natalizumab, mitoxantrone, glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, and fingolimod. There is also 1 available symptomatic MS therapy to improve walking, prolonged-release fampridine, known as dalfampridine extended release in the United States.

5.5. Profile of Previous Experience with BIIB033

5.5.1. Nonclinical Experience

BIIB033 is a fully human aglycosylated immunoglobulin G1 (IgG1) monoclonal antibody that binds LINGO-1 with high affinity. As LINGO-1 is a cell surface glycoprotein selectively expressed in CNS oligodendrocytes and neurons that prevents myelination of axons by oligodendrocytes, a blockade of LINGO-1 may enhance remyelination and repair in CNS demyelinated lesions.

BIIB033 binds LINGO-1 with high affinity in humans, monkeys, rats, and mice; has high specificity for LINGO-1 and does not cross react with other LINGO family members; enhances differentiation of primary rat, monkey, and human oligodendrocytes in vitro; enhances axonal myelination in an in vitro rat dorsal root ganglion/oligodendrocyte precursor cell co-culture bioassay; has reduced Fcγ and complement effector functions compared to wild-type IgG1; and is efficacious in animal models using biochemical and functional readouts. These data suggest that BIIB033 will be an effective therapy to enhance remyelination in patients with MS.

An assessment of BIIB033 toxicology has been carried out in repeated-dose studies in rats and cynomolgus monkeys, as these species are considered pharmacologically relevant based on sequence homology with LINGO-1 and/or similarity in binding and in vitro functional activity with LINGO 1. Toxicology studies of up to 6 months in duration did not identify any adverse treatment-related effects or any effect on neurobehavioral assessments with weekly IV administrations of BIIB033 at up to an maximum feasible dose (MFD) of 316 mg/kg or 3-time-per week subcutaneous (SC) doses at up to 32 mg/kg. Effects on the CNS and respiratory system were transient, and none were considered adverse responses to BIIB033. In embryo-fetal toxicology studies in rats and rabbits, BIIB033 was shown to be not causing fetal abnormalities at maternal doses up to 316 mg/kg. Maternal toxicity and morbidity were noted in 1 rabbit given 316 mg/kg, but the relationship to BIIB033 treatment was unclear; no maternal toxicity was observed in rats at any dose.

Immunohistochemical analyses have identified target and nontarget antigen-specific cross-reactivity by fluorescein isothiocyanate-conjugated BIIB033 (FITC-BIIB033)-specific staining in a range of human, cynomolgus monkey, and rat tissues, including those of neural, epithelial, neuroendocrine, and connective tissue origins. Consistent BIIB033-specific immunostaining using 2 concentrations of FITC-BIIB033 was observed in the brain (primarily, the cerebral cortex) and spinal cord across all 3 species, and the pattern of FITC-BIIB033-specific staining was consistent with that of LINGO-1 protein localization, as previously observed in rodents. Additional non-neural tissues with inconsistent binding patterns across species were evaluated within the repeated-dose toxicology studies and were not identified as target organs of toxicity associated with BIIB033 administration up to an MFD dose over 6 months of treatment. The exposure-based safety margin for the highest dose planned for chronic dosing in the clinic (100 mg/kg/month) is projected to be 4- to 6-fold lower relative to exposures at the no-observed-adverse-effect level in toxicology species after 6 months of dosing.

Together, these data support ongoing evaluations of BIIB033 in Phase 2 studies.

See the IB for detailed information on nonclinical studies.

5.5.2. Clinical Experience

As of 07 May 2015, 72 healthy volunteers (54 BIIB033 and 18 placebo) have been dosed in a single-ascending-dose (SAD) clinical study (Study 215HV101), 47 subjects with MS (32 BIIB033 and 15 placebo) have been dosed in a multiple-ascending-dose (MAD) clinical study (Study 215MS101), 82 subjects with AON (41 BIIB033 and 41 placebo) have been dosed in a Phase 2 Study 215ON201, and 418 subjects with MS (treatment groups still blinded) have been dosed in the ongoing Phase 2 Study 215MS201.

Overall, BIIB033 has been well tolerated in clinical studies. In the completed Study 215HV101 (SAD), which evaluated the safety, tolerability, and pharmacokinetics (PK) of BIIB033 in healthy volunteers, doses ranging from 0.1 to 100 mg/kg BIIB033 were administered to a total of 54 healthy adult volunteers. There were no serious adverse events (SAEs) in the SAD study. Most adverse events (AEs) considered related to study treatment in the SAD study were mild, except for 3 moderate events (2 cases of headache and 1 case of gastroenteritis). The most common AEs with an incidence of ≥5% reported by subjects receiving BIIB033 were headache (10 subjects [19%]), upper respiratory tract infection (6 subjects [11%]), nasopharyngitis (4 subjects [7%]), and gastroenteritis (3 subjects [6%]). Overall, the frequency of AEs was similar between the BIIB033 and placebo groups.

In the completed Study 215MS101 (MAD), which evaluated the safety, tolerability, and PK of BIIB033 in subjects with RRMS or SPMS, multiple doses ranging from 0.3 to 100 mg/kg BIIB033 were administered to a total of 32 subjects. There were no SAEs in the MAD study. The frequency of AEs was similar in BIIB033-treated subjects compared with placebo-treated subjects. The most common AEs with an incidence of ≥5% reported by subjects receiving BIIB033 were headache and urinary tract infection (5 subjects [16%] each), upper respiratory

tract infection and MS relapse (3 subjects [9%] each), and postlumbar puncture headache (2 subjects [6%]).

The completed Phase 2 Study 215ON201 was designed to assess the efficacy, safety, tolerability, and PK of BIIB033 in subjects with their first episode of AON. In this study, the dose of 100 mg/kg BIIB033 was well tolerated, and the overall incidence of AEs was the same in the placebo and BIIB033 groups (34 subjects [83%] in each group). The most common AEs with an incidence of ≥10% reported by subjects receiving BIIB033 were nasopharyngitis (12 subjects [29%]), headache (11 subjects [27%]), fatigue (6 subjects [15%]), nausea (5 subjects [12%]), and paresthesia (4 subjects [10%]). There were 7 of 82 subjects (9%) who experienced SAEs, 5 subjects (12%) in the BIIB033 treatment group and 2 subjects (5%) in the placebo group. In the BIIB033 treatment group, 3 subjects had SAEs that were considered related to study treatment by the Investigator: 2 subjects with hypersensitivity reactions occurring during study treatment infusions and 1 subject with asymptomatic increased aspartate aminotransferase, increased alanine aminotransferase, and liver disorder. Two subjects in the BIIB033 treatment group experienced SAEs considered not related to study treatment. These included 1 subject with MS relapse and 1 subject with optic neuritis. All of the SAEs in the BIIB033 treatment group were reported as resolved. No anti-BIIB033 antibodies were seen in Study 215ON201, except for 1 subject who tested positive at predose baseline.

The reported events of hypersensitivity (serious and nonserious) in the clinical studies have occurred after the start of either the first or the second study treatment infusion in both Phase 1 and 2 studies. In all cases, the infusions were stopped, appropriate treatment was administered, and all events resolved.

The Phase 2 Study, 215MS201, was designed to assess the efficacy, safety, tolerability, and PK of BIIB033 in subjects with relapsing forms of MS when used concurrently with Avonex and is currently ongoing. In this study, the most common AEs with an incidence of ≥10% in the combined BIIB033 and placebo treatment groups are influenza like illness (175 subjects [42%]), MS relapse (123 subjects [29%]), headache (68 subjects [16%]), upper respiratory tract infection (51 subjects [12%]), urinary tract infection (46 subjects [11%]), pyrexia (44 subjects [11%]), and nasopharyngitis (40 subjects [10%]). Fifty of 418 subjects enrolled (12%) reported SAEs as of 07 May 2015. SAEs that were reported in more than 1 subject included MS relapse (27 subjects [6%]), urinary tract infection (3 subjects [<1%]), and hypersensitivity (4 subjects [<1%]). As this study is still ongoing, the treatment codes are blinded, and it is not known if the events occurred in subjects treated with BIIB033 or placebo.

BIIB033 PK following a single dose (IV and SC) up to 100 mg/kg in healthy volunteers and 2 repeated IV doses up to 100 mg/kg in subjects with MS was characterized in the SAD and MAD studies, respectively. BIIB033 PK appears to be similar between healthy volunteers and subjects with MS. In general, BIIB033 PK was linear with small volume of distribution at steady state, minimal target-mediated clearance, and an elimination half-life of approximately 2 to 3 weeks. As expected, the CSF/serum concentration ratio for BIIB033 in humans is estimated to be approximately 0.1%. In the Phase 2 Study 215ON201, the preliminary PK results suggest that

the predicted BIIB033 pharmacological exposure at 100 mg/kg was achieved in subjects with AON, and BIIB033 PK appears to be similar to healthy adults and subjects with MS.

Please refer to the BIIB033 IB for additional details and results on clinical studies.

5.6. Study Rationale

A biological effect of BIIB033 was shown in Study 215ON201 in subjects with AON. In this study, subjects received 6 doses of 100 mg/kg BIIB033 or placebo administered via IV infusion every 4 weeks up to Week 20, with Follow-Up Visits at Weeks 24 and 32. Efficacy results showed an improvement in mean change in full-field visual evoked potential (FF-VEP) latency values of the affected eye from the baseline of the fellow eye at Week 24 in the BIIB033 group compared with placebo in the intent-to-treat population (-3.48 [95% confidence interval (CI): -10.61, 3.65] msec, analysis of covariance [ANCOVA]). The treatment effect was more pronounced in the per-protocol population (-7.55 [95% CI: -15.12, 0.01] msec, ANCOVA). The electrophysiologic differences between the treatment and placebo groups, first observed at Week 12 during the dosing period, persisted throughout the subsequent monthly dosing visits.

The change in FF-VEP latency in the affected eye versus the baseline of the unaffected fellow eye by mixed model for repeated measures (MMRM) showed a greater treatment effect at Week 32 than at Week 24 for both the intent-to-treat (ITT) and per-protocol populations, despite subjects completing the dosing period at Week 20. In the ITT population, an improvement of -6.06 msec over placebo was seen in the BIIB033 group at Week 32 by MMRM ($p = 0.0711$). A significant improvement of -9.13 msec over placebo was seen in the BIIB033 group at Week 32 in the per-protocol population by MMRM ($p = 0.0112$).

Study 215ON201 also showed that all subjects, regardless of assigned treatment, recovered clinically to a large extend regardless of treatment assignment or severity of injury to the retina or the optic nerve; however, not all subjects demonstrated complete functional recovery upon electrophysiologic examination. The rationale for the discrepancy between clinical recovery and electrophysiological improvement is unclear and requires further investigation.

Given these data, the proposed follow-up study is necessary to assess the long-term electrophysiologic and clinical outcomes of this patient population with past randomized exposure to remyelinating therapy versus placebo, but also to explore potential mechanism(s) by which patients recover from previous AON. This information will be critical in the ongoing clinical development of remyelinating therapies so that they can be optimally evaluated and utilized for maximal benefit.

Please refer to the BIIB033 IB for additional details and results on Study 215ON201.

5.7. Rationale for Dosing Regimen

No study drug dosing is planned for this follow-up study.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to assess FF-VEP latency in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit.

The primary endpoint that is related to this objective is the change in FF-VEP latency of the affected eye as compared to the baseline of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201.

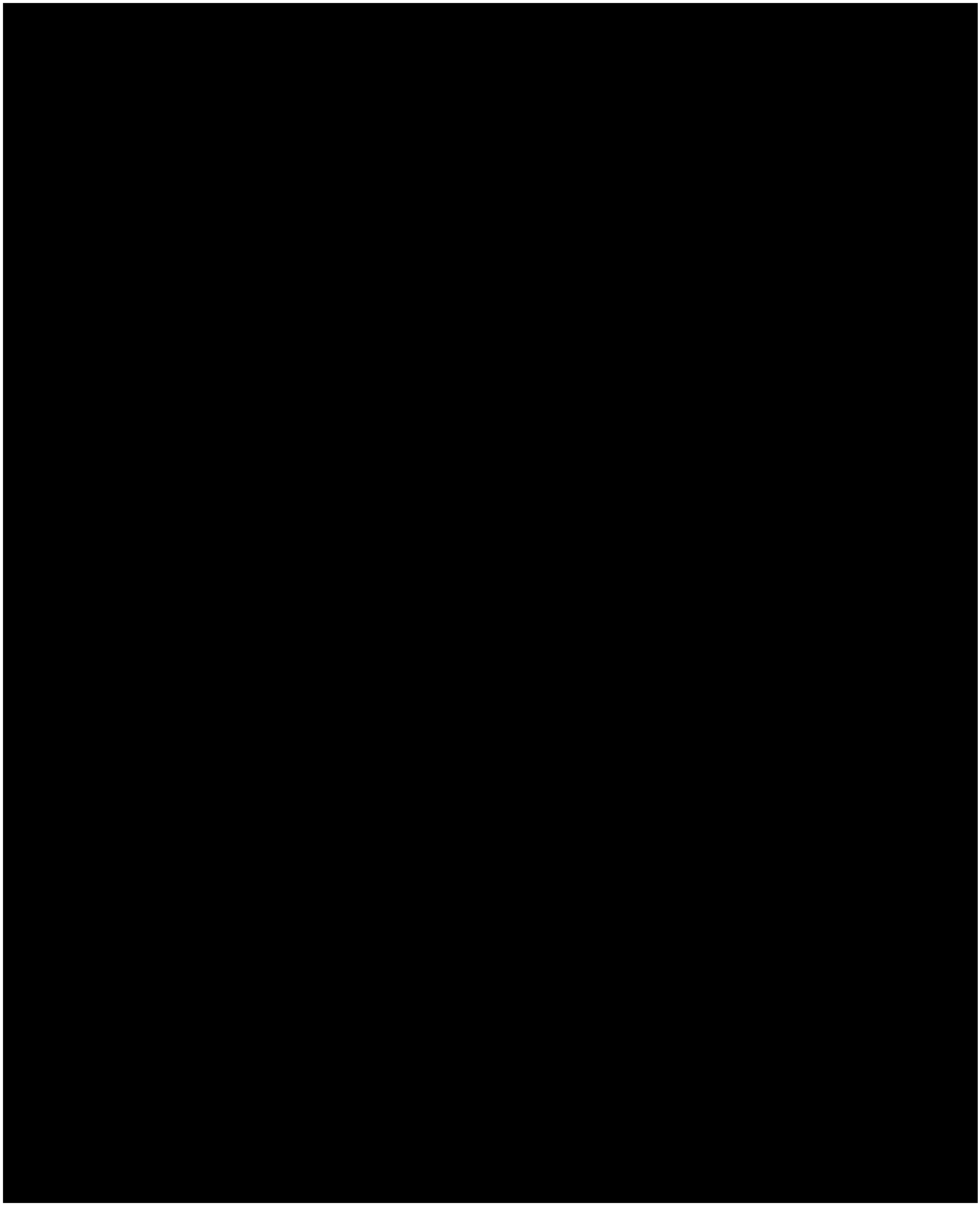
6.2. Secondary Objectives and Endpoints

The secondary objective is to assess clinical progression and severity of CNS demyelinating disease in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit.

The endpoints that relate to this objective are as follows:

- Evaluate incidence of CDMS and time to diagnosis of CDMS.
- Evaluate severity of CNS demyelinating disease with Expanded Disability Status Scale (EDSS) and multiple sclerosis functional composite (MSFC).
- Evaluate change in disease activity from baseline with brain MRI with and without gadolinium (Gd). MRI analysis will include the following:
  - Number of Gd-enhanced lesions
  - Volume of T2 lesions

[redacted]



7. STUDY DESIGN

7.1. Study Overview

This multicenter, follow-up study will determine the long-term electrophysiologic and clinical outcomes in subjects previously enrolled in Study 215ON201.

One group is planned, with eligible subjects (previously enrolled in Study 215ON201) having been already administered at least 1 study treatment (BIIB033 100 mg/kg or placebo) by IV infusion once every 4 weeks for 20 weeks (a total of 6 doses). Dosing was completed 2 years (+ 4 months) prior to enrollment in this follow-up study. A maximum of 82 subjects (determined from the number of subjects who received at least 1 dose of BIIB033 or placebo in Study 215ON201) will be included in this study. There is no formal sample size calculation. The number of subjects eligible for this study is determined by the number of subjects who participated in Study 215ON201.

See Figure 1 for a schematic of the study design.

7.2. Overall Study Duration

The study period will consist of an approximately 1-day visit (with a +5-day window of the 1-day visit) that is dependent on the scanner capabilities and equipment availability at each clinical site.

7.2.1. Screening

Subject eligibility for the study will be determined by the date of 2 years (+ 4 months) after the last study visit (Week 32) or projected Week 32 visit, if the subject did not complete all visits in Study 215ON201. There is no screening visit in this study.

7.2.2. Treatment

No study drug dosing is planned for this study.

7.2.3. Visit Schedule

Each subject will have approximately 1 scheduled study visit (with a +5-day window of the 1-day visit) that is dependent on the scanner capabilities and equipment availability at each clinical site.

7.3. Study Stopping Rules

Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

7.4. End of Study

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

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of Day 1 visit or at the timepoint specified in the individual eligibility criterion listed:

1. Must have participated in Study 215ON201 and received at least 1 dose of BIIB033 or placebo, as per protocol, within 2 years (+ 4 months) from Day 1 of this study (2 years from Week 32 or projected Week 32 visit, if the subject did not complete all visits in Study 215ON201).

2. 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.

8.2. Exclusion Criteria

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

1. Not previously enrolled in Study 215ON201.

2. Inability to comply with study requirements.

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

4. Subjects with recent kidney function, such as serum creatinine above upper limit of normal range, will not be allowed to receive administration of Gd but will otherwise be allowed to participate in the study, including MRI assessments not requiring the use of Gd.

5. Female subjects must have had a recent pregnancy test and must not be breastfeeding prior to MRI assessments with Gd.

9. ENROLLMENT AND REGISTRATION

9.1. Enrollment

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any study-related tests are performed (see Section 15.3). When a subject signs the informed consent form (ICF), that subject is considered to be enrolled 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 enrolment log.

9.2. Registration of Subjects

Subjects will be registered at 2 years (+ 4 months) after their last study visit (Week 32) or projected Week 32 visit, if the subjects did not complete all visits in Study 215ON201, and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2.

Refer to the Study Reference Guide for details on registration.

9.3. Blinding Procedures

This is a follow-up study with no investigational product, therefore blinding is not applicable. As much as possible, the treatment disclosure for Study 215ON201 should not be shared with sites or patients until the end of this study to reduce the risk of bias on the follow on assessments based on knowledge of treatment.

10. WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Sponsor or Investigator for medical reasons or for noncompliance.

The reason for the subject's withdrawal from the study must be recorded in the subject's case report form (CRF).

11. FOLLOW-UP ASSESSMENTS

See Section 4 for the timing of all assessments.

11.1. One-Day Visit Assessments

This study will assess the electrophysiological function of the visual pathway using FF-VEP. The various electrophysiologic and imaging measurements will be made to assess feasibility of being utilized as potential clinical endpoints sensitive to remyelination therapy in multicenter clinical studies (Table 1). Clinical progression and severity of disease will be assessed by the following:

- Medical history, including date of diagnosis of CDMS
- MS diagnosis
- MS signs and symptoms
- Concomitant therapy and procedures recording
- Vital signs
- Physical examination
- EDSS
- MSFC
- [redacted]
- [redacted]
- FF-VEP
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- SAEs related to study procedure(s) reporting

12. SAFETY ASSESSMENTS

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

12.1. Safety Assessments

The following assessments will be performed to evaluate the safety profile related to study procedure(s):

- Physical examinations
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate
- SAEs related to study procedure(s)

12.2. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The definitions of these clinically relevant abnormalities are shown in Table 2.

Table 2: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C
Pulse	>100 bpm <40 bpm
Systolic Blood Pressure	>160 mmHg <90 mmHg
Diastolic Blood Pressure	>100 mmHg <45 mmHg

bpm = beats per minute.

13. SAFETY DEFINITIONS, CLASSIFICATIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible SAEs related to study procedure(s). If an SAE 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 must be given the names and telephone numbers of study site staff for reporting SAEs and medical emergencies.

13.1. Definition

13.1.1. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.

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

13.2. Safety Classifications

13.2.1. 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 13.1.1.
- The relationship of the event to the study procedure(s).

- The severity of the event as defined in Section 13.2.3.

13.2.2. Relationship of Events to Study Procedure(s)

The following definitions should be considered when evaluating the relationship of SAEs to the study procedure(s).

Relationship of Event to Study Procedure(s)	
Not related	An SAE will be considered "not related" to the study procedure(s) if there is not a reasonable possibility that the event has been caused by the study procedure(s). Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between study procedure(s) and the event, the presence of a biologically implausible relationship between the study procedure(s) and the SAE, or the presence of a more likely alternative explanation for the SAE.
Related	An SAE will be considered "related" to the study procedure(s) if there is a reasonable possibility that the event may have been caused by the study procedure(s). Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between study procedure(s) and the event, a known response pattern of the study procedure(s), a biologically plausible relationship between the study procedure(s) and the SAE, or a lack of an alternative explanation for the SAE.

13.2.3. Severity of Events

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

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of study procedure(s); treatment for symptoms may be given and/or subject hospitalized.

13.3. Monitoring and Recording Events

13.3.1. Serious Adverse Events

Any SAE experienced by a subject post ICF sign-off through end-of-study visit and considered by the Investigator to be related to study procedure(s) is to be recorded on an SAE form, regardless of the severity of the event. Information on SAEs related to study procedure(s) must

be reported to [redacted] within 24 hours as described in Section 13.3.2. Follow-up information regarding an SAE also must be reported with 24 hours.

Subjects will be followed for all SAEs until the event has resolved, stabilized, or returned to baseline status.

13.3.2. 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 [redacted] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs
Any SAE related to study procedure that occurs between post ICF sign-off through end-of-study visit must be reported to [redacted] within 24 hours of the study site staff becoming aware of the event. 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.

13.3.2.1. Deaths

Death is an outcome of an event. The procedure-related event that resulted in death should be recorded on the appropriate CRF and reported as an SAE 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 [redacted]. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

13.3.3. Suspected Unexpected Serious Adverse Reactions

Not applicable as no study treatment will be administered.

13.3.4. 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's Official Study Contact List for complete contact information.

13.4. Safety Responsibilities

13.4.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all SAEs that are deemed to be related to the study procedure(s).
- Determine the relationship and severity of each event.
- Determine the onset and resolution dates of each event.
- Complete an SAE form for each procedure-related SAE and fax it to [redacted] within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently until the event has resolved or become stable. Follow-up information must be reported to [redacted] within 24 hours of the study site staff becoming aware of new information.
- Ensure all SAE reports are supported by documentation in the subjects' medical records.
- Report SAEs to local ethics committees, as required by local law.

13.4.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor is responsible for reviewing with study site staff the definition of SAEs, as well as the instructions for monitoring, recording, and reporting procedure-related SAEs.
- Biogen is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of procedure-related SAEs, as required by local law, within required time frames.

14. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

14.1. Efficacy

14.1.1. Analysis Population

Analysis of efficacy endpoints will be based on all enrolled subjects who complete the 1-day assessments.

14.1.2. General Methods of Analysis

Unless stated otherwise, summary statistics will be presented by original treatment groups and overall. For continuous endpoints, the summary statistics will generally include number of subjects enrolled, number of subjects evaluated, mean, standard deviation, median, and range. For categorical endpoints, the summary statistics will generally include number of subjects enrolled, number of subjects evaluated, and the percent of subjects in each category.

14.1.2.1. Analysis of the Primary Endpoint

The primary analysis will be on the change in FF-VEP latency of the affected eye as compared to the baseline (measured prior to dosing in Study 215201) of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201. The ANCOVA model will be used to test the difference between the 2 original treatment groups from Study 215ON201, adjusting for the baseline of the unaffected fellow eye.

14.1.2.2. Analysis of the Secondary Endpoints

The secondary endpoints will include the time to diagnosis of CDMS, severity of disease evaluated by EDSS and MSFC, and brain MRI results. Number and percentage of subjects with diagnosis of CDMS will be summarized, and descriptive statistics of time to diagnosis of CDMS will be presented. EDSS, MSFC, and brain MRI outcomes will also be summarized using descriptive statistics.

[redacted]

14.2. Safety

14.2.1. Analysis Population

The safety population is defined as all enrolled subjects who complete the 1-day assessments.

14.2.2. Methods of Analysis

All SAEs, clinical laboratory abnormalities, vital sign measurements, and physical examination findings will be evaluated for safety.

14.2.2.1. Serious Adverse Events

SAEs will be coded using the Medical Dictionary for Regulatory Activities. The incidence of clinical SAEs will be summarized by severity and by relationship to study procedure(s). The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class.

14.2.2.2. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The definitions of these clinically relevant abnormalities are shown in Table 2.

14.3. Interim Analyses

An interim analysis will be performed when approximately 50% of potentially projected available subjects have been enrolled into the study to provide information to assist the interpretation and design of ongoing clinical development of CNS remyelinating therapies. Statistical analyses listed in Section 14.1 will be performed on primary, secondary, and [redacted] endpoints at the interim analysis.

14.4. Sample Size Considerations

The sample size is based on the number of subjects who participated in Study 215ON201 (approximately 82) rather than statistical considerations. The subjects eligible for this study must have participated in Study 215ON201.

15. ETHICAL REQUIREMENTS

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

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

15.1. Declaration of Helsinki

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

15.2. 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 all countries where subjects are enrolled.

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.

15.3. Subject Information and Consent

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

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

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

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

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

15.4. Subject Data Protection

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

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

15.5. Compensation for Injury

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

15.6. 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.

15.7. 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.

16. ADMINISTRATIVE PROCEDURES

16.1. Study Site Initiation

The Investigator must not enroll any subjects prior to completion of an on-site or remote study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

16.2. Quality Assurance

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

16.3. Monitoring of the Study

No site may initiate the 1-day assessments until Biogen or its designee representatives have concluded protocol-specific training and approved assessment technitian(s).

Biogen or its designee representatives may conduct on-site visits at the study facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to subject (or associated) source files for the purpose of verifying entries made in the CRF and assist with their activities, if requested. Adequate space and time for monitoring visits should be made available by the Investigator or study staff. The site must complete the CRFs in a timely manner and on an ongoing basis to allow regular review by the study team.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

16.4. 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.

16.5. Publications

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

17. FURTHER REQUIREMENTS AND GENERAL INFORMATION

17.1. External Contract Organizations

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

17.1.1. Contract Research Organization

[redacted], a contract research organization (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 enrolled at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

17.1.2. Electronic Data Capture

Subject information will be captured and managed by study sites on CRFs via an appropriate Web-based electronic remote data capture tool.

17.1.3. Central Facility for Other Assessments

A central facility has been selected by Biogen to be a central reader for [redacted], FF-VEP, and [redacted] for this study. A separate central facility has been selected by Biogen to read and interpret all MRI results for this study.

17.2. 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 15).

17.3. 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.

17.4. Retention of Study Data

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

17.5. Study Report Signatory

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

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

18. REFERENCES

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19. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

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PROTOCOL NUMBER: 215ON203

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201

EUDRA CT NO: 2015-003618-26

DATE: 26 August 2015
Version 1.0
Final

SPONSOR SIGNATURE

Protocol 215ON203 was approved by:

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

26 August 2015
Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. 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 Manual for the full contact information of the Medical Monitor.

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

2. LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
AON	acute optic neuritis
CDMS	clinically definite multiple sclerosis
CI	confidence interval
CIS	clinically isolated syndrome
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
[redacted]	[redacted]
EDSS	Expanded Disability Status Scale
FITC-BIIB033	fluorescein isothiocyanate-conjugated BIIB033
FF-VEP	full-field visual evoked potential
[redacted]	[redacted]
GCP	Good Clinical Practice
Gd	gadolinium
IB	Investigator's Brochure
IP	Investigational product
HCVA	high-contrast visual acuity
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN-β	interferon-beta
IgG1	immunoglobulin G1
ITT	intent-to-treat
IV	intravenous
LCLA	low-contrast letter acuity
MAD	multiple-ascending dose
MFD	maximum feasible dose
[redacted]	[redacted]
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite
[redacted]	[redacted]
[redacted]	[redacted]
NEI-VFQ-25	25-item National Eye Institute Visual Function Questionnaire
[redacted]	[redacted]
PK	pharmacokinetic(s)

RGCL	retinal ganglion cell layer
RNFL	retinal nerve fiber layer
[redacted]	[redacted]
RRMS	relapsing-remitting multiple sclerosis
SAD	single-ascending dose
SAE	serious adverse event
SC	subcutaneous
[redacted]	[redacted]
SPMS	secondary progressive multiple sclerosis

3. SYNOPSIS

Protocol Number:	215ON203
Protocol Title:	A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201
Version Number:	1.0
Study Indication:	Acute optic neuritis (AON)
Study Rationale:	BIIB033 (human anti-LINGO-1 monoclonal antibody) is an investigational product with the potential of enhancing remyelination and neuroaxonal protection. In Study 215ON201, treatment of patients with AON with BIIB033 displayed evidence of functional remyelination in the affected eye by demonstrating significant improvement in visual evoked potential latency over treatment with placebo. The electrophysiologic differences between the treatment and placebo groups were first observed at Week 12 during the dosing period and persisted throughout the subsequent monthly dosing visits. More interestingly, this trend continued for an additional 3 months through the Follow-Up Visit at Week 32 despite subjects completing the dosing period at Week 20. Study 215ON201 also showed that all subjects, regardless of assigned treatment, recovered clinically to a large extent regardless of treatment assignment or severity of injury to the retina or the optic nerve; however, not all subjects demonstrated complete functional recovery upon electrophysiologic examination. The rationale for the discrepancy between clinical recovery and electrophysiological improvement is unclear and requires further investigation. Given these data, the proposed follow-up study is necessary to assess the long-term electrophysiologic and clinical outcomes of this patient population with past randomized exposure to remyelinating therapy versus placebo and also to explore potential mechanism(s) by which patients recover

	from previous AON. This information will be critical in ongoing clinical development of remyelinating therapies so that they can be optimally evaluated and utilized for maximal benefit.
Phase of Development:	2
Study Objectives and Endpoints:	The primary objective of this study is to assess full-field visual evoked potential (FF-VEP) latency in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit. The primary endpoint that is related to this objective is the change in FF-VEP latency of the affected eye as compared to the baseline of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201. The secondary objective is to assess clinical progression and severity of central nervous system (CNS) demyelinating disease in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit. The endpoints that relate to this objective are as follows: • Evaluate incidence of clinically definite multiple sclerosis (CDMS) and time to diagnosis of CDMS. • Evaluate severity of CNS demyelinating disease with Expanded Disability Status Scale (EDSS) and multiple sclerosis functional composite (MSFC). • Evaluate change in disease activity from baseline with brain magnetic resonance imaging (MRI) with and without gadolinium (Gd). MRI analysis will include the following: – Number of Gd-enhanced lesions – Volume of T2 lesions [redacted]

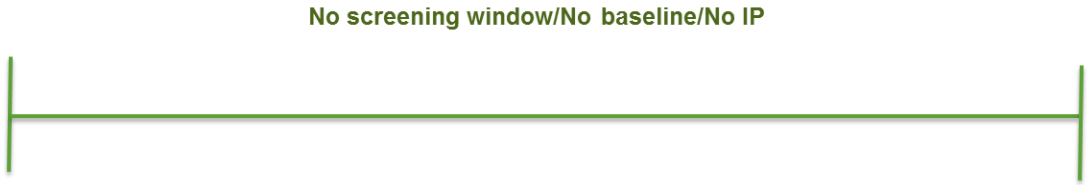
Study Design:	This is a multicenter, follow-up study to determine the long-term electrophysiologic and clinical outcomes in subjects previously enrolled in Study 215ON201. One group is planned, with eligible subjects (previously enrolled in Study 215ON201) having been already administered at least 1 study treatment (BIIB033 100 mg/kg or placebo) by intravenous infusion once every 4 weeks for 20 weeks (a total of 6 doses). Dosing was completed 2 years (+ 4 months) prior to enrollment in this follow-up study. No additional drug or placebo will be administered.
Study Location:	Approximately 33 sites globally are planned.
Number of Planned Subjects:	A maximum of 82 subjects will be eligible for enrollment (determined from the number of subjects who received at least 1 dose of BIIB033 100 mg/kg or placebo in Study 215ON201).
Study Population:	This study will be conducted in subjects who have participated in and received at least 1 dose of BIIB033 or placebo in Study 215ON201. Detailed criteria are described in Section 8.
Duration of Follow-up:	Eligible subjects will be enrolled at 2 years after their last study visit (Week 32) or projected Week 32 (+ 4 months) visit if the subject did not complete all visits in Study 215ON201. Subjects will perform 1 set of follow-up assessments at this timepoint.
Evaluations:	
Safety:	Assessments evaluating the safety profile related to study procedure(s) will include physical examinations, vital sign measurements, and serious adverse events (SAEs). Any SAE experienced by a subject post informed consent form sign-off through end-of-study visit and considered by the Investigator to be related to study procedure(s) is to be recorded on an SAE form, regardless of the severity of the event. Information on SAEs related to study procedure(s) must be reported to [redacted] within 24 hours.

	Subjects will be followed for all SAEs until the event has resolved, stabilized, or returned to baseline status.
Statistical Analysis Methods:	The primary analysis will be on the change in FF-VEP latency of the affected eye as compared to the baseline (measured prior to dosing in Study 215201) of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201. The ANCOVA model will be used to test the difference between the 2 original treatment groups from Study 215ON201, adjusting for the baseline of the unaffected fellow eye. The secondary endpoints will include the time to diagnosis of CDMS, severity of disease evaluated by EDSS and MSFC, and brain MRI results. Number and percentage of subjects with diagnosis of CDMS will be summarized, and descriptive statistics of time to diagnosis of CDMS will be presented. EDSS, MSFC, and brain MRI outcomes will also be summarized using descriptive statistics. [redacted]
Interim Analysis:	An interim analysis will be performed when approximately 50% of potentially projected available subjects have been enrolled into the study to provide information to assist the interpretation and design of ongoing clinical development of CNS remyelinating therapies.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 215ON203

4.1. Study Schematic

Figure 1: Study Design



IP = investigational product; MRI= magnetic resonance imaging.
Note: All assessments should be performed on the same day where possible or within a + 5 day window of the 1-day visit.

4.2. Schedule of Activities

Table 1: Schedule of Activities

Tests and Assessments[1]	Day 1: (2 Years + 4 Months After Week 32 Visit in Study 215ON201 or Projected Week 32 Visit if the Subject Did Not Complete All Visits)
Informed Consent	X
Eligibility Criteria Check	X
Medical History[2]	X
Multiple Sclerosis Diagnosis	X
Multiple Sclerosis Signs and Symptoms	X
Concomitant Therapy and Procedures Recording	X
Vital Signs[3]	X
Physical Examination	X
Expanded Disability Status Scale[4]	X
Multiple Sclerosis Functional Composite	X
[redacted]	
[redacted]	
Full-Field Visual Evoked Potential[6]	X
[redacted]	

Tests and Assessments[1]	Day 1: (2 Years + 4 Months After Week 32 Visit in Study 215ON201 or Projected Week 32 Visit if the Subject Did Not Complete All Visits)
[redacted]	
Serious Adverse Events Related to Study Procedure(s) Reporting[11]	X

[redacted]; MRI = magnetic resonance imaging.

[1] All assessments should be performed on the same day and in the order listed, when possible (or within a + 5 day window of the 1-day visit).

[2] Medical history will be taken from after last study visit in Study 215ON201.

[3] Vital signs include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate (after sitting down for at least 5 minutes).

[4] Expanded Disability Status Scale should be performed by a study certified rater. Where applicable, refer to study manual for instructions.

[redacted]

[6] Sites and technicians must be qualified and approved by the central reader to perform [redacted], full-field visual evoked potential, and [redacted].

[redacted]

[11] Serious adverse events monitoring for events related to study procedure(s) will be reported post informed consent form sign-off through end-of-study visit.

5. INTRODUCTION

BIIB033, a first-in-class human monoclonal antibody directed against LINGO-1, is a negative regulator of myelination and axonal growth. Antagonizing LINGO-1 with BIIB033 has the potential to enhance remyelination and neuroaxonal protection in the central nervous system (CNS).

LINGO-1 is a cell surface glycoprotein that is selectively expressed in the adult CNS in neurons and oligodendrocytes [Barrette 2007; Carim-Todd 2003; Llorens 2008; Mi 2004; Park 2005; Shao 2005]. It functions as a negative regulator of oligodendrocyte differentiation, myelination, and remyelination [Lee 2007; Mi 2005; Mi 2009; Mi 2008]. Axonal and neuronal expression of LINGO-1 increases after injury [Ji 2006; Mi 2004]. LINGO-1 expression prevents myelination of axons by oligodendrocytes.

Several nonclinical studies have demonstrated the potential for LINGO-1 antagonism to enhance CNS remyelination and neuroaxonal protection in animal models of toxic (cuprizone plus rapamycin) [Mi 2009], chemical (lysophosphatidylcholine), and inflammatory (myelin oligodendrocyte glycoprotein-experimental autoimmune encephalomyelitis) [Mi 2007] demyelination and of toxic (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) neuronal [Inoue 2007] and traumatic/hypertensive optic nerve [Fu 2008] and spinal cord [Ji 2008; Ji 2006] injury. The leading hypothesis for this clinical development program is that antagonism of LINGO-1 with BIIB033 will enhance remyelination and neuroaxonal protection in CNS demyelinating diseases such as multiple sclerosis (MS) and acute optic neuritis (AON), leading to CNS improvement with corresponding beneficial effects on neurological function and disability.

Additional details may be found in the BIIB033 Investigator's Brochure (IB).

5.1. Overview of Acute Optic Neuritis

The anterior visual pathway, particularly the optic nerve and its retinal nerve fiber layer (RNFL) and retinal ganglion cell layer (RGCL), is affected by AON and is a potential target for therapeutic compounds with properties to enhance remyelination and neuroaxonal protection. In a study of the long-term effects of AON in the context of MS, the RNFL was decreased to an average of 83 microns [Costello 2006; Talman 2010]. This corresponds to an average loss of ~20 microns or 20% of nerve fibers relative to unaffected eyes in patients with AON or to a loss of ~13 microns relative to eyes in patients with MS without history or presence of AON [Talman 2010]. Costello et al [Costello 2006] found that 74% of patients had 20% or greater thinning of the RNFL following AON. As also noted by Henderson et al [Henderson 2011 Aug], this RNFL thinning begins early (between 1 and 2 months after onset of AON), and nearly all of the eventual RNFL loss is complete by 6 months. This loss of RNFL is associated with a clinically important loss of visual function, as shown by a decrease of low-contrast letter acuity (LCLA) to an average of 21 letters out of 60 or a loss of 14 letters relative to unaffected MS eyes. There is also a permanent loss of visual motion perception in most patients affected by AON [Raz 2011].

Motion processing impairments in AON may be highly disruptive to the ability of patients to ambulate, drive, and navigate [Duffy 2011a; Duffy 2011b]. The permanent loss of visual function in AON is clinically important as reflected by a vision-related quality of life score of 84 on the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), which is 8 points lower than in unaffected patients [Balcer 2012]. This 8-point loss on the NEI-VFQ-25 is higher than the currently accepted 4-point threshold for clinically important changes in vision-related quality of life [Mowry 2009; Submacular Surgery Trials Research Group 2007].

5.2. Current Therapies for Acute Optic Neuritis

The only currently available treatment for AON is high-dose intravenous (IV) steroids (e.g., methylprednisolone) followed by an oral prednisone taper, which speeds up the recovery of symptoms (e.g., ocular pain) and high-contrast visual acuity (HCVA) primarily in the first 2 weeks after an attack, but has no long-term beneficial effects on the ultimate recovery of visual function [Beck 1992] nor is there evidence that it affects the degree of axonal loss or conduction velocity in the optic nerve pathway.

Despite treatment with high-dose steroids, over 60% of patients with AON are left with loss of visual function [Kupersmith 2007].

5.3. Overview of Multiple Sclerosis

MS is a chronic disabling neurological disease that affects an estimated 1 million people in North America and Western Europe. It is a disease of young adults, primarily women, with disease onset typically occurring between the ages of 20 and 40 years [Weinshenker 1989]. It is the most frequent cause of nontraumatic neurological disability affecting young adults in the Western world. Although the etiology is uncertain, evidence suggests that MS is, in part, an autoimmune disease directed against protein components of myelin. The diagnosis of clinically definite multiple sclerosis (CDMS) has traditionally been made on the basis of clinical criteria and requires that a patient experience at least 2 neurologic events consistent with demyelination, separated both in time and in location in the CNS [Poser 1983]. More recent diagnostic criteria have allowed for less than 2 neurologic attacks, when there is supportive laboratory evidence based on magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF) results [McDonald 2001]. The majority of patients with MS start out with a clinical course characterized by episodes or attacks (relapses) of neurologic dysfunction, which occur over many years. This phase of the disease is called relapsing-remitting multiple sclerosis (RRMS). Symptoms of such relapses include loss of vision or double vision, numbness or tingling sensation in the extremities, muscle weakness, slurred speech, difficulty with coordination, and bladder dysfunction. Patients having the first clinical attack are referred to as clinically isolated syndrome (CIS). The most common CIS types are AON, transverse myelitis, and brainstem attack. Patients with CIS with characteristic brain MRI lesions are considered to be having MS by the most recent diagnostic McDonald criteria [Polman 2011]. Patients with CIS without brain lesions are at low risk of developing MS. Early in the course of relapsing MS, the signs and symptoms tend to subside completely after each attack. Over time, there tends to be incomplete recovery from such attacks. The majority of patients with relapsing MS accumulate some

disability, and about half are unable to walk without assistance within 15 years of their initial diagnosis [Runmarker and Andersen 1993; Weinshenker 1989]. The majority of patients with RRMS eventually enter the secondary progressive phase of the disease (secondary progressive multiple sclerosis [SPMS]), characterized by steady worsening of disability independently of relapses. About 15% of the patients go into this progressive phase without prior development of a relapsing-remitting phase and are referred to as having a primary progressive MS.

5.4. Current Therapies for Multiple Sclerosis

Available therapies for the treatment of relapsing MS target the immunomodulation of inflammatory activity and include interferon-beta (IFN-β)1a, pegylated IFN-β1a, IFN-β1b, natalizumab, mitoxantrone, glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, and fingolimod. There is also 1 available symptomatic MS therapy to improve walking, prolonged-release fampridine, known as dalfampridine extended release in the United States.

5.5. Profile of Previous Experience with BIIB033

5.5.1. Nonclinical Experience

BIIB033 is a fully human aglycosylated immunoglobulin G1 (IgG1) monoclonal antibody that binds LINGO-1 with high affinity. As LINGO-1 is a cell surface glycoprotein selectively expressed in CNS oligodendrocytes and neurons that prevents myelination of axons by oligodendrocytes, a blockade of LINGO-1 may enhance remyelination and repair in CNS demyelinated lesions.

BIIB033 binds LINGO-1 with high affinity in humans, monkeys, rats, and mice; has high specificity for LINGO-1 and does not cross react with other LINGO family members; enhances differentiation of primary rat, monkey, and human oligodendrocytes in vitro; enhances axonal myelination in an in vitro rat dorsal root ganglion/oligodendrocyte precursor cell co-culture bioassay; has reduced Fcγ and complement effector functions compared to wild-type IgG1; and is efficacious in animal models using biochemical and functional readouts. These data suggest that BIIB033 will be an effective therapy to enhance remyelination in patients with MS.

An assessment of BIIB033 toxicology has been carried out in repeated-dose studies in rats and cynomolgus monkeys, as these species are considered pharmacologically relevant based on sequence homology with LINGO-1 and/or similarity in binding and in vitro functional activity with LINGO 1. Toxicology studies of up to 6 months in duration did not identify any adverse treatment-related effects or any effect on neurobehavioral assessments with weekly IV administrations of BIIB033 at up to an maximum feasible dose (MFD) of 316 mg/kg or 3-time-per week subcutaneous (SC) doses at up to 32 mg/kg. Effects on the CNS and respiratory system were transient, and none were considered adverse responses to BIIB033. In embryo-fetal toxicology studies in rats and rabbits, BIIB033 was shown to be not causing fetal abnormalities at maternal doses up to 316 mg/kg. Maternal toxicity and morbidity were noted in 1 rabbit given 316 mg/kg, but the relationship to BIIB033 treatment was unclear; no maternal toxicity was observed in rats at any dose.

Immunohistochemical analyses have identified target and nontarget antigen-specific cross-reactivity by fluorescein isothiocyanate-conjugated BIIB033 (FITC-BIIB033)-specific staining in a range of human, cynomolgus monkey, and rat tissues, including those of neural, epithelial, neuroendocrine, and connective tissue origins. Consistent BIIB033-specific immunostaining using 2 concentrations of FITC-BIIB033 was observed in the brain (primarily, the cerebral cortex) and spinal cord across all 3 species, and the pattern of FITC-BIIB033-specific staining was consistent with that of LINGO-1 protein localization, as previously observed in rodents. Additional non-neural tissues with inconsistent binding patterns across species were evaluated within the repeated-dose toxicology studies and were not identified as target organs of toxicity associated with BIIB033 administration up to an MFD dose over 6 months of treatment. The exposure-based safety margin for the highest dose planned for chronic dosing in the clinic (100 mg/kg/month) is projected to be 4- to 6-fold lower relative to exposures at the no-observed-adverse-effect level in toxicology species after 6 months of dosing.

Together, these data support ongoing evaluations of BIIB033 in Phase 2 studies.

See the IB for detailed information on nonclinical studies.

5.5.2. Clinical Experience

As of 07 May 2015, 72 healthy volunteers (54 BIIB033 and 18 placebo) have been dosed in a single-ascending-dose (SAD) clinical study (Study 215HV101), 47 subjects with MS (32 BIIB033 and 15 placebo) have been dosed in a multiple-ascending-dose (MAD) clinical study (Study 215MS101), 82 subjects with AON (41 BIIB033 and 41 placebo) have been dosed in a Phase 2 Study 215ON201, and 418 subjects with MS (treatment groups still blinded) have been dosed in the ongoing Phase 2 Study 215MS201.

Overall, BIIB033 has been well tolerated in clinical studies. In the completed Study 215HV101 (SAD), which evaluated the safety, tolerability, and pharmacokinetics (PK) of BIIB033 in healthy volunteers, doses ranging from 0.1 to 100 mg/kg BIIB033 were administered to a total of 54 healthy adult volunteers. There were no serious adverse events (SAEs) in the SAD study. Most adverse events (AEs) considered related to study treatment in the SAD study were mild, except for 3 moderate events (2 cases of headache and 1 case of gastroenteritis). The most common AEs with an incidence of ≥5% reported by subjects receiving BIIB033 were headache (10 subjects [19%]), upper respiratory tract infection (6 subjects [11%]), nasopharyngitis (4 subjects [7%]), and gastroenteritis (3 subjects [6%]). Overall, the frequency of AEs was similar between the BIIB033 and placebo groups.

In the completed Study 215MS101 (MAD), which evaluated the safety, tolerability, and PK of BIIB033 in subjects with RRMS or SPMS, multiple doses ranging from 0.3 to 100 mg/kg BIIB033 were administered to a total of 32 subjects. There were no SAEs in the MAD study. The frequency of AEs was similar in BIIB033-treated subjects compared with placebo-treated subjects. The most common AEs with an incidence of ≥5% reported by subjects receiving BIIB033 were headache and urinary tract infection (5 subjects [16%] each), upper respiratory

tract infection and MS relapse (3 subjects [9%] each), and postlumbar puncture headache (2 subjects [6%]).

The completed Phase 2 Study 215ON201 was designed to assess the efficacy, safety, tolerability, and PK of BIIB033 in subjects with their first episode of AON. In this study, the dose of 100 mg/kg BIIB033 was well tolerated, and the overall incidence of AEs was the same in the placebo and BIIB033 groups (34 subjects [83%] in each group). The most common AEs with an incidence of ≥10% reported by subjects receiving BIIB033 were nasopharyngitis (12 subjects [29%]), headache (11 subjects [27%]), fatigue (6 subjects [15%]), nausea (5 subjects [12%]), and paresthesia (4 subjects [10%]). There were 7 of 82 subjects (9%) who experienced SAEs, 5 subjects (12%) in the BIIB033 treatment group and 2 subjects (5%) in the placebo group. In the BIIB033 treatment group, 3 subjects had SAEs that were considered related to study treatment by the Investigator: 2 subjects with hypersensitivity reactions occurring during study treatment infusions and 1 subject with asymptomatic increased aspartate aminotransferase, increased alanine aminotransferase, and liver disorder. Two subjects in the BIIB033 treatment group experienced SAEs considered not related to study treatment. These included 1 subject with MS relapse and 1 subject with optic neuritis. All of the SAEs in the BIIB033 treatment group were reported as resolved. No anti-BIIB033 antibodies were seen in Study 215ON201, except for 1 subject who tested positive at predose baseline.

The reported events of hypersensitivity (serious and nonserious) in the clinical studies have occurred after the start of either the first or the second study treatment infusion in both Phase 1 and 2 studies. In all cases, the infusions were stopped, appropriate treatment was administered, and all events resolved.

The Phase 2 Study, 215MS201, was designed to assess the efficacy, safety, tolerability, and PK of BIIB033 in subjects with relapsing forms of MS when used concurrently with Avonex and is currently ongoing. In this study, the most common AEs with an incidence of ≥10% in the combined BIIB033 and placebo treatment groups are influenza like illness (175 subjects [42%]), MS relapse (123 subjects [29%]), headache (68 subjects [16%]), upper respiratory tract infection (51 subjects [12%]), urinary tract infection (46 subjects [11%]), pyrexia (44 subjects [11%]), and nasopharyngitis (40 subjects [10%]). Fifty of 418 subjects enrolled (12%) reported SAEs as of 07 May 2015. SAEs that were reported in more than 1 subject included MS relapse (27 subjects [6%]), urinary tract infection (3 subjects [<1%]), and hypersensitivity (4 subjects [<1%]). As this study is still ongoing, the treatment codes are blinded, and it is not known if the events occurred in subjects treated with BIIB033 or placebo.

BIIB033 PK following a single dose (IV and SC) up to 100 mg/kg in healthy volunteers and 2 repeated IV doses up to 100 mg/kg in subjects with MS was characterized in the SAD and MAD studies, respectively. BIIB033 PK appears to be similar between healthy volunteers and subjects with MS. In general, BIIB033 PK was linear with small volume of distribution at steady state, minimal target-mediated clearance, and an elimination half-life of approximately 2 to 3 weeks. As expected, the CSF/serum concentration ratio for BIIB033 in humans is estimated to be approximately 0.1%. In the Phase 2 Study 215ON201, the preliminary PK results suggest that

the predicted BIIB033 pharmacological exposure at 100 mg/kg was achieved in subjects with AON, and BIIB033 PK appears to be similar to healthy adults and subjects with MS.

Please refer to the BIIB033 IB for additional details and results on clinical studies.

5.6. Study Rationale

A biological effect of BIIB033 was shown in Study 215ON201 in subjects with AON. In this study, subjects received 6 doses of 100 mg/kg BIIB033 or placebo administered via IV infusion every 4 weeks up to Week 20, with Follow-Up Visits at Weeks 24 and 32. Efficacy results showed an improvement in mean change in full-field visual evoked potential (FF-VEP) latency values of the affected eye from the baseline of the fellow eye at Week 24 in the BIIB033 group compared with placebo in the intent-to-treat population (-3.48 [95% confidence interval (CI): -10.61, 3.65] msec, analysis of covariance [ANCOVA]). The treatment effect was more pronounced in the per-protocol population (-7.55 [95% CI: -15.12, 0.01] msec, ANCOVA). The electrophysiologic differences between the treatment and placebo groups, first observed at Week 12 during the dosing period, persisted throughout the subsequent monthly dosing visits.

The change in FF-VEP latency in the affected eye versus the baseline of the unaffected fellow eye by mixed model for repeated measures (MMRM) showed a greater treatment effect at Week 32 than at Week 24 for both the intent-to-treat (ITT) and per-protocol populations, despite subjects completing the dosing period at Week 20. In the ITT population, an improvement of -6.06 msec over placebo was seen in the BIIB033 group at Week 32 by MMRM ($p = 0.0711$). A significant improvement of -9.13 msec over placebo was seen in the BIIB033 group at Week 32 in the per-protocol population by MMRM ($p = 0.0112$).

Study 215ON201 also showed that all subjects, regardless of assigned treatment, recovered clinically to a large extend regardless of treatment assignment or severity of injury to the retina or the optic nerve; however, not all subjects demonstrated complete functional recovery upon electrophysiologic examination. The rationale for the discrepancy between clinical recovery and electrophysiological improvement is unclear and requires further investigation.

Given these data, the proposed follow-up study is necessary to assess the long-term electrophysiologic and clinical outcomes of this patient population with past randomized exposure to remyelinating therapy versus placebo, but also to explore potential mechanism(s) by which patients recover from previous AON. This information will be critical in the ongoing clinical development of remyelinating therapies so that they can be optimally evaluated and utilized for maximal benefit.

Please refer to the BIIB033 IB for additional details and results on Study 215ON201.

5.7. Rationale for Dosing Regimen

No study drug dosing is planned for this follow-up study.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to assess FF-VEP latency in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit.

The primary endpoint that is related to this objective is the change in FF-VEP latency of the affected eye as compared to the baseline of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201.

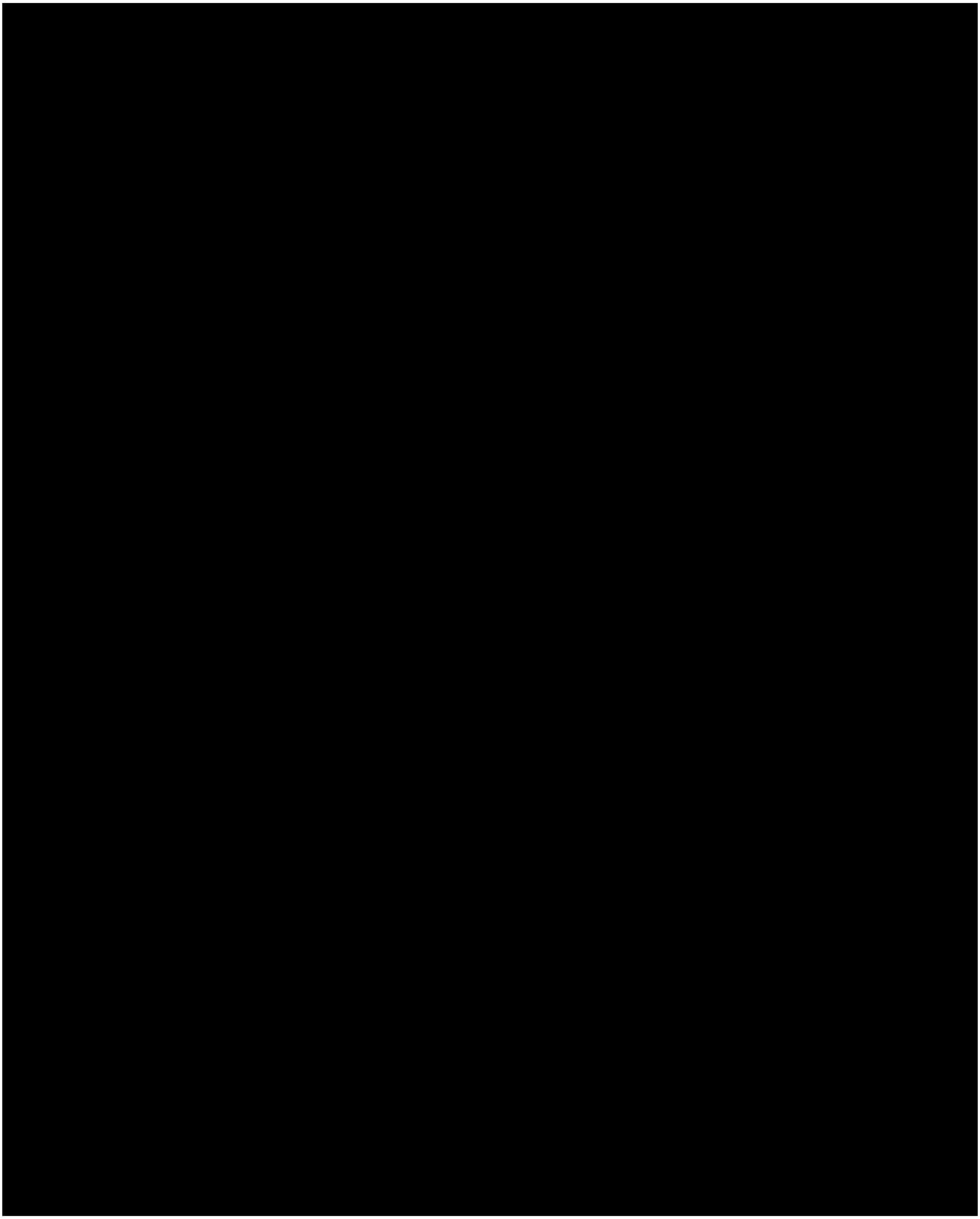
6.2. Secondary Objectives and Endpoints

The secondary objective is to assess clinical progression and severity of CNS demyelinating disease in subjects who were enrolled in Study 215ON201 2 years (+ 4 months) after the last study visit.

The endpoints that relate to this objective are as follows:

- Evaluate incidence of CDMS and time to diagnosis of CDMS.
- Evaluate severity of CNS demyelinating disease with Expanded Disability Status Scale (EDSS) and multiple sclerosis functional composite (MSFC).
- Evaluate change in disease activity from baseline with brain MRI with and without gadolinium (Gd). MRI analysis will include the following:
  - Number of Gd-enhanced lesions
  - Volume of T2 lesions

[redacted]



7. STUDY DESIGN

7.1. Study Overview

This multicenter, follow-up study will determine the long-term electrophysiologic and clinical outcomes in subjects previously enrolled in Study 215ON201.

One group is planned, with eligible subjects (previously enrolled in Study 215ON201) having been already administered at least 1 study treatment (BIIB033 100 mg/kg or placebo) by IV infusion once every 4 weeks for 20 weeks (a total of 6 doses). Dosing was completed 2 years (+ 4 months) prior to enrollment in this follow-up study. A maximum of 82 subjects (determined from the number of subjects who received at least 1 dose of BIIB033 or placebo in Study 215ON201) will be included in this study. There is no formal sample size calculation. The number of subjects eligible for this study is determined by the number of subjects who participated in Study 215ON201.

See Figure 1 for a schematic of the study design.

7.2. Overall Study Duration

The study period will consist of an approximately 1-day visit (with a +5-day window of the 1-day visit) that is dependent on the scanner capabilities and equipment availability at each clinical site.

7.2.1. Screening

Subject eligibility for the study will be determined by the date of 2 years (+ 4 months) after the last study visit (Week 32) or projected Week 32 visit, if the subject did not complete all visits in Study 215ON201. There is no screening visit in this study.

7.2.2. Treatment

No study drug dosing is planned for this study.

7.2.3. Visit Schedule

Each subject will have approximately 1 scheduled study visit (with a +5-day window of the 1-day visit) that is dependent on the scanner capabilities and equipment availability at each clinical site.

7.3. Study Stopping Rules

Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

7.4. End of Study

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

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of Day 1 visit or at the timepoint specified in the individual eligibility criterion listed:

1. Must have participated in Study 215ON201 and received at least 1 dose of BIIB033 or placebo, as per protocol, within 2 years (+ 4 months) from Day 1 of this study (2 years from Week 32 or projected Week 32 visit, if the subject did not complete all visits in Study 215ON201).

2. 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.

8.2. Exclusion Criteria

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

1. Not previously enrolled in Study 215ON201.

2. Inability to comply with study requirements.

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

4. Subjects with recent kidney function, such as serum creatinine above upper limit of normal range, will not be allowed to receive administration of Gd but will otherwise be allowed to participate in the study, including MRI assessments not requiring the use of Gd.

5. Female subjects must have had a recent pregnancy test and must not be breastfeeding prior to MRI assessments with Gd.

9. ENROLLMENT AND REGISTRATION

9.1. Enrollment

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any study-related tests are performed (see Section 15.3). When a subject signs the informed consent form (ICF), that subject is considered to be enrolled 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 enrolment log.

9.2. Registration of Subjects

Subjects will be registered at 2 years (+ 4 months) after their last study visit (Week 32) or projected Week 32 visit, if the subjects did not complete all visits in Study 215ON201, and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2.

Refer to the Study Reference Guide for details on registration.

9.3. Blinding Procedures

This is a follow-up study with no investigational product, therefore blinding is not applicable. As much as possible, the treatment disclosure for Study 215ON201 should not be shared with sites or patients until the end of this study to reduce the risk of bias on the follow on assessments based on knowledge of treatment.

10. WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Sponsor or Investigator for medical reasons or for noncompliance.

The reason for the subject's withdrawal from the study must be recorded in the subject's case report form (CRF).

11. FOLLOW-UP ASSESSMENTS

See Section 4 for the timing of all assessments.

11.1. One-Day Visit Assessments

This study will assess the electrophysiological function of the visual pathway using FF-VEP. The various electrophysiologic and imaging measurements will be made to assess feasibility of being utilized as potential clinical endpoints sensitive to remyelination therapy in multicenter clinical studies (Table 1). Clinical progression and severity of disease will be assessed by the following:

- Medical history, including date of diagnosis of CDMS
- MS diagnosis
- MS signs and symptoms
- Concomitant therapy and procedures recording
- Vital signs
- Physical examination
- EDSS
- MSFC
- [redacted]
- [redacted]
- FF-VEP
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- SAEs related to study procedure(s) reporting

12. SAFETY ASSESSMENTS

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

12.1. Safety Assessments

The following assessments will be performed to evaluate the safety profile related to study procedure(s):

- Physical examinations
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate
- SAEs related to study procedure(s)

12.2. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The definitions of these clinically relevant abnormalities are shown in Table 2.

Table 2: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C
Pulse	>100 bpm <40 bpm
Systolic Blood Pressure	>160 mmHg <90 mmHg
Diastolic Blood Pressure	>100 mmHg <45 mmHg

bpm = beats per minute.

13. SAFETY DEFINITIONS, CLASSIFICATIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible SAEs related to study procedure(s). If an SAE 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 must be given the names and telephone numbers of study site staff for reporting SAEs and medical emergencies.

13.1. Definition

13.1.1. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.

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

13.2. Safety Classifications

13.2.1. 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 13.1.1.
- The relationship of the event to the study procedure(s).

- The severity of the event as defined in Section 13.2.3.

13.2.2. Relationship of Events to Study Procedure(s)

The following definitions should be considered when evaluating the relationship of SAEs to the study procedure(s).

Relationship of Event to Study Procedure(s)	
Not related	An SAE will be considered "not related" to the study procedure(s) if there is not a reasonable possibility that the event has been caused by the study procedure(s). Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between study procedure(s) and the event, the presence of a biologically implausible relationship between the study procedure(s) and the SAE, or the presence of a more likely alternative explanation for the SAE.
Related	An SAE will be considered "related" to the study procedure(s) if there is a reasonable possibility that the event may have been caused by the study procedure(s). Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between study procedure(s) and the event, a known response pattern of the study procedure(s), a biologically plausible relationship between the study procedure(s) and the SAE, or a lack of an alternative explanation for the SAE.

13.2.3. Severity of Events

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

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of study procedure(s); treatment for symptoms may be given and/or subject hospitalized.

13.3. Monitoring and Recording Events

13.3.1. Serious Adverse Events

Any SAE experienced by a subject post ICF sign-off through end-of-study visit and considered by the Investigator to be related to study procedure(s) is to be recorded on an SAE form, regardless of the severity of the event. Information on SAEs related to study procedure(s) must

be reported to [redacted] within 24 hours as described in Section 13.3.2. Follow-up information regarding an SAE also must be reported with 24 hours.

Subjects will be followed for all SAEs until the event has resolved, stabilized, or returned to baseline status.

13.3.2. 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 [redacted] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs
Any SAE related to study procedure that occurs between post ICF sign-off through end-of-study visit must be reported to [redacted] within 24 hours of the study site staff becoming aware of the event. 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.

13.3.2.1. Deaths

Death is an outcome of an event. The procedure-related event that resulted in death should be recorded on the appropriate CRF and reported as an SAE 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 [redacted]. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

13.3.3. Suspected Unexpected Serious Adverse Reactions

Not applicable as no study treatment will be administered.

13.3.4. 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's Official Study Contact List for complete contact information.

13.4. Safety Responsibilities

13.4.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all SAEs that are deemed to be related to the study procedure(s).
- Determine the relationship and severity of each event.
- Determine the onset and resolution dates of each event.
- Complete an SAE form for each procedure-related SAE and fax it to [redacted] within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently until the event has resolved or become stable. Follow-up information must be reported to [redacted] within 24 hours of the study site staff becoming aware of new information.
- Ensure all SAE reports are supported by documentation in the subjects' medical records.
- Report SAEs to local ethics committees, as required by local law.

13.4.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor is responsible for reviewing with study site staff the definition of SAEs, as well as the instructions for monitoring, recording, and reporting procedure-related SAEs.
- Biogen is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of procedure-related SAEs, as required by local law, within required time frames.

14. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

14.1. Efficacy

14.1.1. Analysis Population

Analysis of efficacy endpoints will be based on all enrolled subjects who complete the 1-day assessments.

14.1.2. General Methods of Analysis

Unless stated otherwise, summary statistics will be presented by original treatment groups and overall. For continuous endpoints, the summary statistics will generally include number of subjects enrolled, number of subjects evaluated, mean, standard deviation, median, and range. For categorical endpoints, the summary statistics will generally include number of subjects enrolled, number of subjects evaluated, and the percent of subjects in each category.

14.1.2.1. Analysis of the Primary Endpoint

The primary analysis will be on the change in FF-VEP latency of the affected eye as compared to the baseline (measured prior to dosing in Study 215201) of the fellow eye at 2 years (+ 4 months) after the last study visit assessment (Week 32) in Study 215ON201. The ANCOVA model will be used to test the difference between the 2 original treatment groups from Study 215ON201, adjusting for the baseline of the unaffected fellow eye.

14.1.2.2. Analysis of the Secondary Endpoints

The secondary endpoints will include the time to diagnosis of CDMS, severity of disease evaluated by EDSS and MSFC, and brain MRI results. Number and percentage of subjects with diagnosis of CDMS will be summarized, and descriptive statistics of time to diagnosis of CDMS will be presented. EDSS, MSFC, and brain MRI outcomes will also be summarized using descriptive statistics.

[redacted]

14.2. Safety

14.2.1. Analysis Population

The safety population is defined as all enrolled subjects who complete the 1-day assessments.

14.2.2. Methods of Analysis

All SAEs, clinical laboratory abnormalities, vital sign measurements, and physical examination findings will be evaluated for safety.

14.2.2.1. Serious Adverse Events

SAEs will be coded using the Medical Dictionary for Regulatory Activities. The incidence of clinical SAEs will be summarized by severity and by relationship to study procedure(s). The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class.

14.2.2.2. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The definitions of these clinically relevant abnormalities are shown in Table 2.

14.3. Interim Analyses

An interim analysis will be performed when approximately 50% of potentially projected available subjects have been enrolled into the study to provide information to assist the interpretation and design of ongoing clinical development of CNS remyelinating therapies. Statistical analyses listed in Section 14.1 will be performed on primary, secondary, and [redacted] endpoints at the interim analysis.

14.4. Sample Size Considerations

The sample size is based on the number of subjects who participated in Study 215ON201 (approximately 82) rather than statistical considerations. The subjects eligible for this study must have participated in Study 215ON201.

15. ETHICAL REQUIREMENTS

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

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

15.1. Declaration of Helsinki

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

15.2. 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 all countries where subjects are enrolled.

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.

15.3. Subject Information and Consent

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

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

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

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

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

15.4. Subject Data Protection

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

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

15.5. Compensation for Injury

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

15.6. 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.

15.7. 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.

16. ADMINISTRATIVE PROCEDURES

16.1. Study Site Initiation

The Investigator must not enroll any subjects prior to completion of an on-site or remote study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

16.2. Quality Assurance

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

16.3. Monitoring of the Study

No site may initiate the 1-day assessments until Biogen or its designee representatives have concluded protocol-specific training and approved assessment technitian(s).

Biogen or its designee representatives may conduct on-site visits at the study facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to subject (or associated) source files for the purpose of verifying entries made in the CRF and assist with their activities, if requested. Adequate space and time for monitoring visits should be made available by the Investigator or study staff. The site must complete the CRFs in a timely manner and on an ongoing basis to allow regular review by the study team.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

16.4. 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.

16.5. Publications

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

17. FURTHER REQUIREMENTS AND GENERAL INFORMATION

17.1. External Contract Organizations

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

17.1.1. Contract Research Organization

[redacted], a contract research organization (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 enrolled at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

17.1.2. Electronic Data Capture

Subject information will be captured and managed by study sites on CRFs via an appropriate Web-based electronic remote data capture tool.

17.1.3. Central Facility for Other Assessments

A central facility has been selected by Biogen to be a central reader for [redacted], FF-VEP, and [redacted] for this study. A separate central facility has been selected by Biogen to read and interpret all MRI results for this study.

17.2. 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 15).

17.3. 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.

17.4. Retention of Study Data

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

17.5. Study Report Signatory

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

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

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19. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Multicenter, Follow-Up Study to Assess Long-Term Electrophysiologic and Clinical Outcomes in Subjects Previously Enrolled in Study 215ON201," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

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Study Site (Print)