**COVER PAGE**

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|---|---|
| **Official Title:** | An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation |
| **NCT number:** | NCT03070119 |
| **Document Date:** | 04 Aug 2021 |

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**PROTOCOL NUMBER:** 233AS102

**PHASE OF DEVELOPMENT:** 3

**PROTOCOL TITLE:** An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation

**EUDRA CT NO:** 2016-003225-41

**DATE:** 04 August 2021
Version 6
**FINAL**
Supersedes previous Version 5 dated 08 November 2019

# SPONSOR SIGNATURE PAGE

Protocol 233AS102 was approved by:

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Date

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# 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 Guide's Official Study Contact List for complete contact information.

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

# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALS | amyotrophic lateral sclerosis |
| [redacted] | [redacted] |
| ALSFRS-R | Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised |
| aPTT | activated partial thromboplastin time |
| ASO | antisense oligonucleotide |
| AUC | area under the concentration-time curve |
| [redacted] | [redacted] |
| CI | confidence interval |
| CMAP | compound muscle action potential |
| CNS | central nervous system |
| CRF | case report form |
| CSF | cerebrospinal fluid |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DHA | Directions for Handling and Administration |
| DNA | deoxyribonucleic acid |
| DPS | diaphragm pacing system |
| ECG | electrocardiogram |
| EEG | electroencephalogram |
| [redacted] | [redacted] |
| GCP | Good Clinical Practice |
| HED | human equivalent dose |
| HHD | handheld dynamometry |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IDMC | independent data monitoring committee |
| INR | international normalized ratio |
| IRT | interactive response technology |
| IT | intrathecal |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| mITT | modified intention-to-treat |
| mRNA | messenger ribonucleic acid |
| [redacted] | [redacted] |
| NfL | neurofilament light chain |
| NHP | non-human primate |
| NOAEL | no observed adverse effect level |
| [redacted] | [redacted] |
| PD | pharmacodynamic(s) |
| [redacted] | [redacted] |
| PHI | protected health information |

| | |
|---|---|
| PK | pharmacokinetic(s) |
| [redacted] | [redacted] |
| PT | prothrombin time |
| RNA | ribonucleic acid |
| SAD | single ascending dose |
| SAE | serious adverse event |
| [redacted] | [redacted] |
| SOD1 | superoxide dismutase 1 |
| SOD1-ALS | amyotrophic lateral sclerosis with a confirmed superoxide dismutase 1 mutation |
| SUSAR | suspected unexpected serious adverse reaction |
| SVC | slow vital capacity |
| $t_{½}$ | elimination half-life |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

# 3. SYNOPSIS

| | |
|---|---|
| Protocol Number: | 233AS102 |
| Protocol Title: | An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation |
| Version Number | 6 |
| Name of Study Treatment: | BIIB067 |
| Study Indication: | SOD1-ALS |
| Study Rationale | This study is an extension of Study 233AS101, a Phase 1/2/3 study evaluating the benefit/risk of BIIB067. This study will evaluate the long-term safety, tolerability, PK, PD, biomarker effects, and efficacy of BIIB067 administered to participants with SOD1-ALS. |
| Phase of Development: | 3 |
| Study Objectives and Endpoints: | <u>Primary Objective and Endpoint</u><br>The primary objective of the study is to evaluate the long-term safety and tolerability of BIIB067 in participants with ALS and confirmed SOD1 mutation.<br>The associated primary endpoint is the incidence of AEs and SAEs.<br><u>Secondary Objectives and Endpoints</u><br>The secondary objectives are to evaluate the PK, PD, biomarker effects, and efficacy of BIIB067 administered to participants with ALS and confirmed SOD1 mutation.<br>The endpoints include the following:<br>• PK endpoints: Plasma and CSF levels of BIIB067<br>• PD endpoint: Change from baseline in total SOD1 protein in CSF<br>• Biomarker endpoint: Change from baseline in NfL concentration in plasma |

- Efficacy endpoints:
  - Changes over time in the following:
    - Total ALSFRS-R score
    - SVC
    - HHD Megascore and individual muscle strength
  - Time to death or permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days)
  - Time to death

The exploratory objectives and endpoints are listed in Section 6.3.

| | |
|---|---|
| Study Design: | This is a multicenter, long-term extension study of BIIB067. The study will include a 29-day Loading Dose Period, during which participants will receive 3 IT injections approximately every 2 weeks (on Days 1, 15, and 29).<br><br>Participants who have completed Parts A or B of Study 233AS101 will have an unblinded Loading Dose Period, during which they will receive 3 doses of BIIB067.<br><br>Participants who have completed Part C of Study 233AS101 will have a blinded Loading Dose Period, during which participants who received BIIB067 in Study 233AS101 will receive 2 doses of BIIB067, on Days 1 and 29, and placebo on Day 15, and participants who received placebo in Study 233AS101 will receive 3 doses of BIIB067, on Days 1, 15, and 29.<br><br>For all participants, the Loading Dose Period will be followed by an unblinded maintenance dose portion of the study, during which participants will receive up to 90 doses of BIIB067, approximately every 4 weeks. |
| Study Location: | Approximately 42 sites are planned in approximately 15 countries globally. |
| Number of Planned Participants: | The sample size of this extension study is based on the sample size of the SOD1-ALS population in |

| | |
|---|---|
| | Study 233AS101. Up to 183 participants will be dosed in Study 233AS101. |
| Study Population: | This study will be conducted in participants at least 18 years of age with SOD1-ALS who have completed Study 233AS101.<br><br>Detailed criteria are described in Section 8. |
| Treatment Groups: | BIIB067 100 mg will be administered by IT injection. |
| Duration of Study Participation: | The total duration of study participation for a single participant will vary and be up to 368 weeks, consisting of an approximately 4-week screening period; up to a 360-week treatment period; and a 4-week follow-up period. |

# 4. SCHEDULE OF ACTIVITIES FOR STUDY 233AS102

## Table 1: Schedule of Activities

| Assessments | Screening Visit[1] | Baseline/1st Loading Dose Visit | | | 2nd Loading Dose Visit | | | 3rd Loading Dose Visit | | | Maintenance Dose Visit | | | Final or Early Termination Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week -4 to Day -1 | Day 1 | | | Day 15 (±3 days) (Week 2) | | | Day 29 (±3 days) (Week 4) | | | Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 360 (±3 days) | | | 4 weeks after last dose |
| | | Pre dose | LP | Post dose | Pre dose | LP | Post dose | Pre dose | LP | Post dose | Pre dose | LP | Post dose | |
| ICF (main) and Genetic/Future Scientific Research Consent (optional)[2] | X | | | | | | | | | | | | | |
| Medical History | X | X | | | | | | | | | | | | |
| Confirmation of Eligibility Criteria[3] | X | | | | | | | | | | | | | |
| Ventilation Use[4] | X | X | | | X | | | X | | | X | | | X |
| ALSFRS-R | | X[5] | | | X[5] | | | X[5] | | | X[5, 6] | | | X[5] |
| SVC[7] | | X[5] | | | X[5] | | | X[5] | | | X[5, 8] | | | X[5] |
| HHD | | X[5] | | | X[5] | | | X[5] | | | X[5, 8] | | | X[5] |
| [redacted] | | | | | | | | | | | | | | |
| C-SSRS[12] | | X | | | | | | X | | | X[6] | | | X |

| **Assessments** | **Screening Visit[1]** | **Baseline/1st Loading Dose Visit** | | | **2nd Loading Dose Visit** | | | **3rd Loading Dose Visit** | | | **Maintenance Dose Visit** | | | **Final or Early Termination Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Week -4 to Day -1** | **Day 1** | | | **Day 15 (±3 days) (Week 2)** | | | **Day 29 (±3 days) (Week 4)** | | | **Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 360 (±3 days)** | | | **4 weeks after last dose** |
| | | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | |
| Weight | X | X | | | | | | | | | | | | X |
| Vital Signs (temperature, blood pressure, pulse rate, respiratory rate) | X | X | | X | X | | X | X | | X | X | | X | X |
| 12-lead ECG[13] | X | X | | | | | | | | | | | | X |
| Physical Examination[14] | X | X | | | | | | | | | | | | X |
| Limited Neurological Examination[14] | X | X | | | | | | | | | | | | X |
| Pregnancy Test[15] | X | X | | | X | | | X | | | X | | | X |
| CSF Samples[16] | | X[17] | | | X[17] | | | X[17] | | | X[17] | | | |
| Clinical Laboratory Samples for Hematology, Coagulation, Chemistry, and Urinalysis[3] | X | X | | | X | | | X | | | X | | | X |
| [redacted] | | | | | | | | | | | | | | |
| Blood Samples for Plasma anti-BIIB067 Antibody | | X | | | X | | | X | | | X[18] | | | X |
| Blood Samples for PK | | X | | | X | | | X | | | X[18] | | | X |
| Blood Samples for PD and Biomarkers | | X | | | X | | | X | | | X | | | X |
| Blood Samples for DNA[19] | | | | | | | | | | | X | | | |
| Blood Samples for RNA Analysis (optional)[20] | | X | | | X | | | X | | | X | | | X |
| Study Treatment Administration | | | X | | | X | | | X | | | X | | |

| Assessments | Screening Visit[1] | Baseline/1st Loading Dose Visit | | | 2nd Loading Dose Visit | | | 3rd Loading Dose Visit | | | Maintenance Dose Visit | | | Final or Early Termination Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week -4 to Day -1 | Day 1 | | | Day 15 (±3 days) (Week 2) | | | Day 29 (±3 days) (Week 4) | | | Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 360 (±3 days) | | | 4 weeks after last dose |
| | | Pre dose | LP | Post dose | Pre dose | LP | Post dose | Pre dose | LP | Post dose | Pre dose | LP | Post dose | |
| AE/Concomitant Therapy and Procedures Recording | | ----------X (ongoing)---------- | | | | | | | | | | | | |
| SAE Recording | ----------X (ongoing)---------- | | | | | | | | | | | | | |

[1] Screening assessments can be performed over ~2 days (need not be consecutive) to minimize participant burden.

[2] The main ICF will include a genetic consent for collection of DNA samples to confirm presence of SOD1 mutation and to be used for analyses of specific genes related to ALS or the response to BIIB067. DNA and RNA collection for possible future research will be optional in all regions where not prohibited by regulatory authorities or ethics committees. Consent for possible future research (optional) will be collected in a separate document.

[3] The results of the most recent centrally read coagulation tests and platelet count (i.e., those obtained at the previous visit) must be reviewed before LP is performed. Should these results suggest, in the opinion of the Investigator, that LP may be safely performed, then no further review of coagulation tests and platelet counts would be required before performing the LP. However, should repeat coagulation and platelet tests be clinically indicated in the opinion of the Investigator, then these tests may be done locally, to facilitate timely review.

[4] Participants will use a diary/eDiary to record ventilation use. The diary/eDiary should be completed only for days when the participant uses mechanical ventilation. This diary will be reviewed with study site staff at each visit. Refer to the Study Reference Guide for details.

[5] May be performed at any time on the day prior to study treatment administration, predose on the day of study treatment administration, or at the Final or Early Termination Visit.

[6] To be performed at Week 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 272, 276, 280, 284, 288, 292, 296, 300, 304, 308, 312, 316, 320, 324, 328, 332, 336, 340, 344, 348, 352, 356, and 360 Visits (i.e., every 4 weeks).

[7] If a facemask is used in Study 233AS101 or at screening and/or baseline of this study, it should be used for all SVC assessments for the duration of the study. If a facemask is not used during Study 233AS101 or at screening and/or baseline of this study, it should not be used for the duration of the study, if possible. If the participant begins the 233AS102 study not using a facemask but develops the need to use a facemask to complete the SVC during the study, then the facemask should be used for all subsequent SVC assessments for the duration of the study. Upright SVC will be determined by performing 3 to 5 measures. The results will be overread by a central reader to confirm that these criteria (at least 3 acceptable tests with the 2 highest acceptable [largest and next largest] efforts within 150 mL of vital capacity) have been achieved.

[8] To be performed at Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, 312, 324, 336, 348, and 360 (i.e., every 12 weeks) Visits only.

[redacted]

[12]"Since Last Visit" version of C-SSRS will be used after the Baseline/First Loading Dosing Visit.
[13]ECGs to be done at Screening, Day 1, Final/Early Termination Visit, and as clinically necessary per the discretion of the Investigator throughout the study. ECGs will be obtained after participants have rested in a supine position for at least 10 minutes.
[14]A physical examination and limited neurological examination will be performed at the specified timepoints (Screening, Day 1, Final/Early Termination Visit). At all other visits, the physical and/or limited neurological examination may be performed at the Investigator's discretion. The components of the limited neurological examination are coordination/cerebellar function, reflexes, and motor system.
[15]To be performed only in women of childbearing potential; results must be negative to continue participation in study. On dosing days, samples must be analyzed before study treatment administration. To be performed via urine or serum testing.
[16]CSF samples will be collected during the LP for PK, PD, safety, and biomarker analysis and will be analyzed to evaluate for blood contamination. CSF samples for safety will be tested at local laboratories.
[17]Participants will remain under observation in the clinic for ~1 hour after the LP procedure for safety monitoring and can be discharged at the discretion of the Investigator and in compliance with the institutional requirements, once the participants have adequately recovered from the procedure. Participants will receive a safety follow-up telephone contact ~24 hours after the procedure.
[18]Blood samples will be collected on every alternate visit at Week 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148, 156, 164, 172, 180, 188, 196, 204, 212, 220, 228, 236, 244, 252, 260, 268, 276, 284, 292, 300, 308, 316, 324, 332, 340, 348, and 356 (i.e., every 8 weeks) Visits only. Blood samples for anti-BIIB067 antibody and PK assessments will be collected at the same time.
[19]For participants who did not have the presence or absence of a SOD1 mutation confirmed centrally in Study 233AS101, a one-time blood sample will be collected. For participants who did not have a blood sample collected for testing of other genes related to ALS and/or the response to BIIB067 in Study 233AS101, an additional blood sample will be collected. Participants undergoing this sample collection will be asked to sign an optional consent for use of DNA for possible future research in all regions where not prohibited by regulatory authorities or ethics committee.
[20]Participants who agree to provide samples will need to sign separate consent form(s). RNA sample collection for possible future research will be optional in all regions where not prohibited by regulatory authorities or ethics committees.

# 5. INTRODUCTION

BIIB067 is an investigational second-generation ASO inhibitor of SOD1 mRNA, under development to reduce levels of SOD1 protein in patients with SOD1-ALS. ASOs are short synthetic strings of nucleotides designed to prevent the expression of a targeted protein by selectively binding to the mRNA that encodes the protein with high affinity and selectivity through well-characterized Watson-Crick base pairing (hybridization).

## 5.1. Overview of Amyotrophic Lateral Sclerosis

ALS is a rare neurodegenerative disease resulting in loss of motor neurons within the cortex, brainstem, and spinal cord. Patients suffer gradual loss of muscle mass, strength, and function in bulbar, respiratory, and voluntary muscle. Decline is inevitable, with death from respiratory failure following 2 to 5 years after diagnosis for most patients. Although the majority of patients suffer from sporadic ALS, a smaller fraction of patients, approximately 2%, have an inherited, or familial, form of ALS caused by a variety of mutations in SOD1 (referred to as SOD1-ALS) [ALSoD 2015; Ferlay 2013]. During the time since SOD1-ALS was first described in 1993, more than 180 SOD1 mutations have been reported to cause this form of ALS. Disease progression for individual mutations is variable, with survival of less than 15 months seen with the most severe mutations [Cudkowicz 1997].

Overexpression of mutant SOD1 in mice or rats recapitulates important aspects of ALS in humans [Bruijn and Cleveland 1996; Gurney 1994]; however, loss of SOD1, while resulting in eventual motor neuron dysfunction, does not result in motor neuron death [Fischer 2012; Reaume 1996]. Furthermore, neither loss nor increase of SOD1 activity in mouse models of SOD1-ALS alters survival [Bruijn 1998]. In humans, individual disease mutations are associated with varying levels of SOD1 activity; some patients with disease-causing mutations have apparently normal SOD1 activity [Howlader 2015]. Thus, correlation between disease severity and normal SOD1 activity has not been observed [Andersen 1997; Howlader 2015; Ratovitski 1999]. In contrast, reduction of SOD1 with intracerebroventricular-delivered SOD1 ASO extended survival in a rodent model of SOD1-ALS [Smith 2006]. These observations strongly suggest that SOD1-ALS is caused by toxic properties of the mutant SOD1 protein. Reducing SOD1 mRNA and, subsequently, toxic SOD1 protein may offer therapeutic benefit for patients with SOD1-ALS. IT delivery of an ASO targeting SOD1 mRNA is a viable method to reduce toxic SOD1 protein.

## 5.2. Current Therapies for Amyotrophic Lateral Sclerosis

The only currently approved treatments for ALS are riluzole and edaravone, with approvals varying in each region. Riluzole provides a modest increase in survival (2 to 3 months) without noticeable improvement in strength or disability [Miller 2012]. Edaravone lessens functional decline as measured by the ALSFRS-R. The effect of edaravone on survival is unknown [Writing Group and Edaravone (MCI-186) ALS 19 Study Group 2017]. No specific treatments for SOD1-ALS are available.

## 5.3. Profile of Previous Experience With BIIB067

### 5.3.1. Nonclinical Experience

Four in vivo nonclinical toxicology studies were performed to support the development of BIIB067: a repeated-dose, 12-week, subcutaneous bolus injection study in mice (25 and 150 mg/kg); a single-dose, IT bolus injection study in rats (0.1, 0.3, 1.0, and 3.0 mg); a repeated-dose, 13-week, IT bolus injection study in cynomolgus monkeys (4, 12, and 35 mg); and a repeated-dose, 9-month, IT bolus injection study in cynomolgus monkeys (4, 12, and 35 mg).

See the BIIB067 Investigator's Brochure for detailed information on all nonclinical studies.

#### 5.3.1.1. Toxicology

In mice, subcutaneous administration of BIIB067 was well tolerated, with the highest dose evaluated (150 mg/kg) being the NOAEL. The NOAELs in the toxicology studies in which the clinical route of administration (IT) was used were 1 mg (rat) and 35 mg (monkey).

In rats, a single IT bolus delivery of BIIB067 resulted in 1 early death in a rat receiving the highest dose evaluated (3 mg). Transient acute tactile hypersensitivity was noted approximately 25 minutes postdose in animals receiving 3 mg. Decreases in arousal, gait, mobility, respiration, and sensorimotor observations were also noted 3 hours postdose in the 3-mg group.

In cynomolgus monkeys, repeated IT administration of BIIB067 for 13 weeks was well tolerated up to the highest dose evaluated (35 mg), although 2 animals in the 35-mg group had transient clinical signs (reduced locomotor activity). Cytoplasmic vacuolation in some neurons of the hippocampus, and to a lesser degree of the cerebral cortex, was observed at all doses (4, 12, and 35 mg). The neuronal vacuolation was not associated with any morphological evidence of cell degeneration or necrosis and was fully reversible within a 13-week recovery period. Furthermore, IT injection of BIIB067 caused mononuclear inflammatory cell infiltrates in the meninges at the lumbar spinal cord injection site, possibly as a local proinflammatory effect caused by ribonuclease H-based ASOs. Remnants of such inflammatory infiltrates were still detectable after 13 weeks of recovery, although at a lower magnitude. In addition, vacuolated histiocytes were found in lymph nodes as well as in the Virchow-Robin space of the brain; this finding was not fully reversible within 13 weeks. Neuronal vacuolation in the spinal cord was observed in 1 recovery animal but was not observed in any animal at the end of the 13-week dosing period. The relation of this finding to BIIB067 is unknown. Based on the lack of any evidence of cell degeneration or necrosis and absence of clinical or neurological abnormalities associated with the vacuolation, it was concluded that the microscopic findings were not adverse.

From the 9-month cynomolgus monkey toxicology study, the NOAEL for repeated, IT-administered BIIB067 was 12 mg. This was based on adverse clinical observations for 1 female administered 35 mg. This female exhibited neurological signs after the second dose, characterized by transient muscle cramping (seen immediately after dosing on multiple days), prolonged recovery from anesthesia, and intermittent tremors (during the last months of the dosing phase). Treatment with diazepam was required on several dosing occasions. An EEG on

this animal revealed altered postdose signals (with effects on high frequency bands) but confirmed that muscle cramping during EEG recording was not a seizure and could have been related to arousal. This finding was considered test-article related; however, there were no correlates in clinical and anatomic pathology.

#### 5.3.1.2. Pharmacokinetics

To characterize the PK properties of BIIB067, CSF (monkey only), plasma (monkey and mouse only), and tissue (monkey, mouse, and rat) concentrations were assessed following IT (monkey and rat) or subcutaneous (mouse) administration.

Following bolus IT administration in monkeys, BIIB067 concentrations in CSF declined in a multiphasic manner with a rapid distribution phase, followed by a slower and longer elimination phase. The rapid distribution phase was due to rapid and broad distribution from CSF to CNS tissues and clearance from CSF due to transfer to systemic circulation (including plasma and systemic tissues such as kidney and liver). The estimated CSF $t_{½}$ was 20 to 37 days.

BIIB067 concentrations in plasma peaked 1 to 4 hours after the IT bolus injection in monkeys and then rapidly declined during the first 48 hours postdose, with a much slower elimination phase thereafter. The estimated plasma $t_{½}$ was 22 to 51 days. In mice, BIIB067 concentrations in plasma peaked 0.5 hour after subcutaneous administration, indicating rapid absorption into the systemic circulation and, similar to monkeys, declined rapidly over the next 48 hours due to extensive distribution to systemic tissues.

Dose-dependent tissue distribution of BIIB067 to CNS and peripheral tissues was seen in all species studied (monkey, rat, and mouse), with no clear or consistent evidence of a sex difference in distribution to tissues.

Following IT administration, distribution to CNS tissues was broad in both rats and monkeys, with the highest CNS concentrations seen in the lumbar spinal cord, consistent with the IT route of administration. In monkeys, relatively higher concentrations were observed in the liver and kidney, indicating a significant proportion of the administered dose was distributed from CSF to the systemic circulation. During the recovery period, BIIB067 appeared to be cleared slowly from CNS and peripheral tissues. The estimated tissue $t_{½}$ was similar to that for CSF and plasma (31 to 40 days in CNS tissues, 15 to 20 days in the liver, and 18 to 23 days in the kidney). BIIB067 was rapidly and extensively distributed from plasma to liver and kidney following subcutaneous administration in mice.

The long CSF and CNS tissue $t_{½}$ observed in monkeys support an infrequent clinical dosing regimen following IT administration.

### 5.3.2. Clinical Experience

This study is an extension of Study 233AS101, a Phase 1/2/3 study evaluating the benefit/risk of BIIB067. In the single and multiple dose escalation parts (Parts A and B) of this study, BIIB067 at dose levels up to and including 100 mg was generally well tolerated. Most of the AEs were

mild or moderate in severity. Plasma concentrations of BIIB067 were dose proportional; CSF concentrations showed a less-than-dose-proportional response. Administration of BIIB067 100 mg for 12 weeks in Part B of Study 233AS101 led to a 36% reduction in total CSF SOD1 protein compared to a 3% reduction observed in the placebo arm. Administration of BIIB067 100 mg for 12 weeks also led to an apparent slowing in decline across exploratory clinical outcome measures including ALSFRS-R, SVC, and HHD Megascore.

## 5.4. Study Rationale

This study will evaluate the long-term safety, tolerability, PK, PD, and efficacy of BIIB067 administered to participants with SOD1-ALS who have completed Parts A, B, or C of Study 233AS101 of BIIB067.

## 5.5. Rationale for Dosing Regimen

BIIB067 100 mg will be administered via IT bolus over 1 to 3 minutes.

The BIIB067 dosing regimens for Parts A and B of Study 233AS101 were selected based on target tissue concentrations from SOD1 transgenic mouse models, and nonclinical toxicology and PK observations in repeated dose, IT administration in 13-week and 9-month NHP studies.

Based on pharmacology and PK results in SOD1 transgenic mice, the estimated tissue concentrations of BIIB067 needed to produce a 50%, and the upper 95% CI of an 80%, SOD1 mRNA reduction within the human spinal cord are 0.9 µg/g and 4.7 µg/g, respectively. Evaluations of cortex from the same experiment indicate that the estimated tissue concentration of BIIB067 needed to produce a 50% cortical SOD1 mRNA reduction is 8 µg/g.

The lowest dose selected for Study 233AS101 (10 mg in Part A) was predicted to achieve greater than 0.9 µg/g tissue concentration in the spinal cord. The initial highest proposed dose (60 mg, multiple doses in Part B) was predicted to achieve greater than 4.7 µg/g steady-state tissue concentration in the spinal cord, and approximately 1.5 µg/g steady-state tissue concentration in the cortex, which is expected to yield approximately 15% to 20% SOD1 mRNA reduction in that tissue. The addition of a 100-mg cohort is predicted to achieve steady-state exposures in the cortex of approximately 2.5 µg/g, which is predicted to be sufficient for a meaningful CSF total SOD1 protein reduction of 25% to 30%. This reduction is expected to be clinically meaningful, based on the expectation that the reduction of total SOD1 protein in tissues (spinal cord and cortex) would be greater than the 20% to 30% reduction observed in CSF. This prediction is based on observations in NHP studies, where approximately 50% reduction in CSF corresponded to approximately 50% or greater reduction in the spinal cord and cortex. In rodent efficacy experiments, doses of BIIB067 that reduced tissue total SOD1 protein by approximately 30% or more were found to improve measures of electrophysiology, function, and neurofilament.

Based on nonclinical PK and pharmacology data, and taking into consideration participant safety, the inconvenience of repeated IT injections, and the rapid, fatal nature of ALS, the following dose intervals were selected for this extension study: 3 loading doses, once every 2 weeks, and 22 maintenance doses, administered approximately every 4 weeks from Months 3

to 24. These intervals were selected based on the estimated $t_{½}$ of BIIB067 (~1 month) in the target CNS tissues (spinal cord and brain cortex), to achieve and maintain the target tissue concentration of BIIB067 at a steady-state level and within the estimated pharmacologically active range and allow collection of PK and PD data during dose interruption and resumption, providing information on the dynamic behavior of the system.

From the 9-month NHP toxicology study, the NOAEL for repeated, IT-administered BIIB067 was 12 mg. This NOAEL was converted to a HED based on the NHP to human CSF volume scaling (approximately 10-fold difference). CSF volume scaling conservatively estimates the needed scaling factor and has predicted HED with reasonable accuracy. The HED for the 9-month, IT NHP toxicology study was calculated to be 120 mg. This provides a 6-fold safety margin for the BIIB067 starting dose (20 mg) of the extension study, and a 2-fold safety margin for the 60-mg dose. The safety margin for a 100-mg clinical dose (highest planned dose) would be 1.2-fold. Preliminary PK data (plasma AUC from time 0 to 24 hours) from the 20 mg MAD cohort in Study 233AS101, indicate that the safety margin based on exposure is 2.2-fold relative to a 100-mg clinical dose. The 1.2-fold safety margin based on CSF volume scaling from the NHP toxicology study was chosen over the 2.2-fold safety margin calculated from the plasma steady-state exposures, since the former provides a more conservative estimate.

For Part C (Pivotal) of Study 233AS101, the dose of BIIB067 100 mg was determined based on the interim analyses of data from participants in Part B (MAD) Cohorts 5 to 8 treated for 85 days. Safety analyses of these data suggested that all doses through 100 mg had been well tolerated, with a safety profile supportive of continued development of BIIB067 in participants with ALS. The selection of the BIIB067 100 mg dose for Part C is supported by PK/PD [redacted] analyses of data from participants in Part A (SAD) and Part B (MAD) [see Section 5.3.2].

# 6. STUDY OBJECTIVES AND ENDPOINTS

## 6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the long-term safety and tolerability of BIIB067 in participants with ALS and a confirmed SOD1 mutation.

The associated primary endpoint is the incidence of AEs and SAEs.

## 6.2. Secondary Objectives and Endpoints

The secondary objectives are to evaluate the PK, PD, biomarker effects, and efficacy of BIIB067 administered to participants with ALS and a confirmed SOD1 mutation.

### 6.2.1. Pharmacokinetic Endpoints

The PK endpoints are plasma and CSF levels of BIIB067.

### 6.2.2. Pharmacodynamic Endpoint

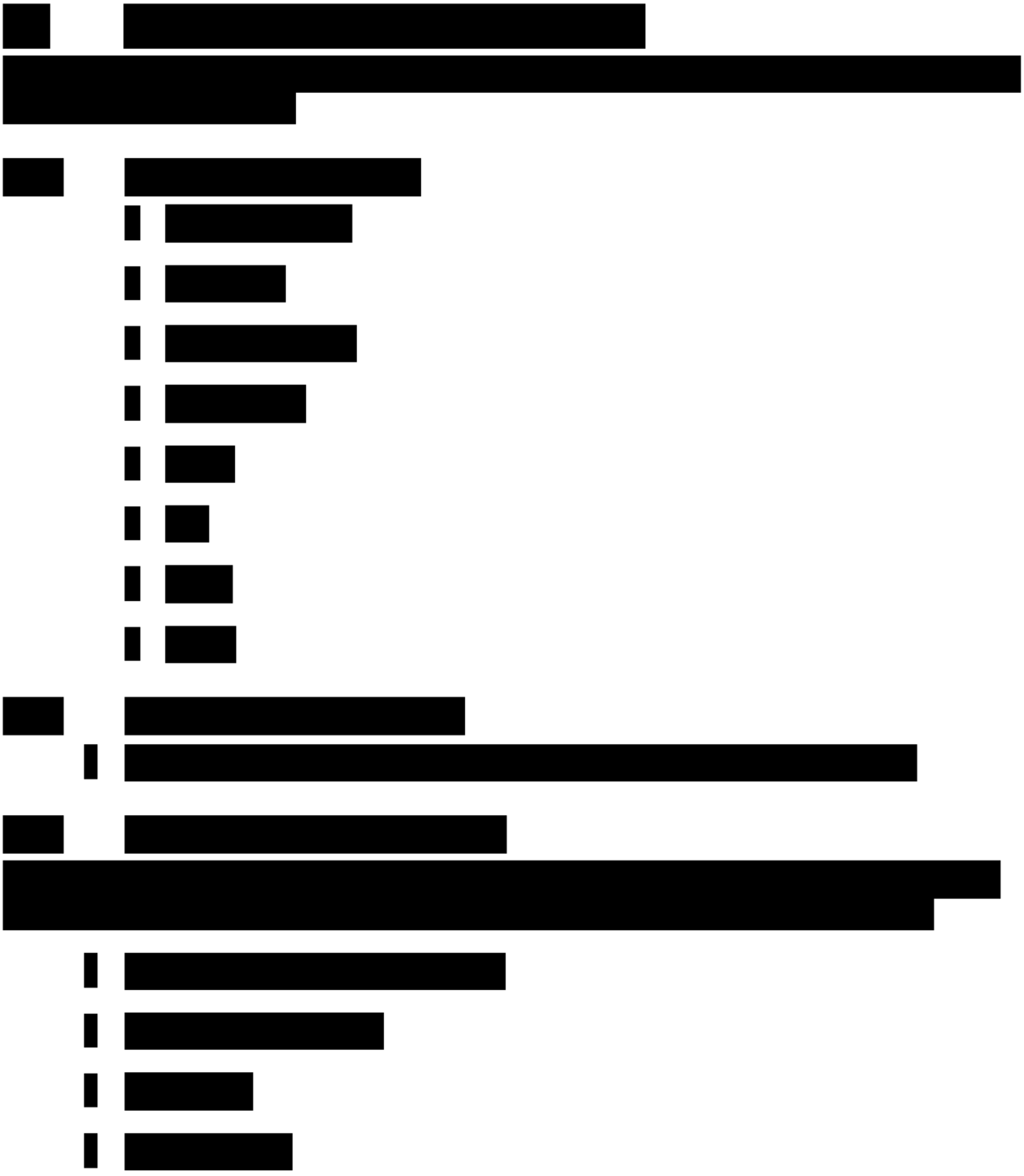
The PD endpoint is the change from baseline in total SOD1 protein in CSF.

### 6.2.3. Biomarker Endpoint

The biomarker endpoint is the change from baseline in NfL concentration in plasma.

### 6.2.4. Efficacy Endpoints

- Efficacy endpoints are changes over time in the following:
  - Total ALSFRS-R score
  - SVC
  - HHD Megascore and individual muscle strength
- Time to death or permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days)
- Time to death



# 7. STUDY DESIGN

## 7.1. Study Overview

This is a multicenter, open-label, long-term extension study to assess the long-term safety, tolerability, PK, PD, and efficacy of BIIB067 administered by IT injection to previously treated participants with SOD1-ALS who have completed Parts A, B, or C of Study 233AS101. The study will be conducted at approximately 42 sites in approximately 15 countries globally.

Participants who have completed Parts A or B of Study 233AS101 will have a washout period of at least 4 times the $t_{½}$ (~16 weeks) from the time of their last dose of study treatment in Study 233AS101 to their first dose in Study 233AS102. These participants will receive 3 loading doses of BIIB067 100 mg, approximately 2 weeks apart, during the first 4 weeks.

Participants who have completed Part C of Study 233AS101 will not have a washout period. To preserve the blinding used in Study 233AS101 until database lock, participants who enroll in Study 233AS102 after completing Part C of Study 233AS101 will have a blinded Loading Dose Period. Participants who received placebo while in Study 233AS101 will receive 3 doses of BIIB067 100 mg, approximately once every 2 weeks (Days 1, 15, and 29), while participants who received BIIB067 in Study 233AS101 will receive 2 doses of BIIB067 100 mg, on Days 1 and 29, and placebo on Day 15.

After the Loading Dose Period, participants will receive up to 90 maintenance doses of BIIB067 100 mg, approximately every 4 weeks until the last participant enrolled has had the opportunity to have their Week 152 Maintenance Dose Visit. Participants who were not receiving BIIB067 100 mg (i.e., participants in Parts A and B) will be dosed at BIIB067 100 mg at their next scheduled Maintenance Dose Visit.

## 7.2. Overall Study Duration and Follow-Up

The overall duration of study participation for a single participant will be up to 368 weeks, which includes an approximately 4-week screening period, up to a 360-week treatment period, and a 4-week follow-up period.

### 7.2.1. Screening

#### 7.2.1.1. Participants Who Have Completed Parts A and B of Study 233AS101

Participants who have completed Part B (MAD) of Study 233AS101 and participants who have completed Part A (SAD) of that study will be eligible for screening. Participant eligibility for the study will be determined from Week -4 through Day -1.

The Screening Visit assessments may be performed over approximately 2 days, which do not need to be consecutive, to minimize participant burden. All assessments must be completed on or before the Baseline/Loading Dose Visit on Day 1.

#### 7.2.1.2. Participants Who Have Completed Part C of Study 233AS101

Participants who have completed the last dosing visit in Part C of Study 233AS101 will be able to screen to determine eligibility to participate in Study 233AS102. A participant's last dosing visit in Part C of Study 233AS101 may be the start of the Screening Visit (Week -4 to Day -1) for this extension Study 233AS102. Results from assessments completed by participants at the last dosing visit of Study 233AS101 can be used for the purpose of screening and do not need to be repeated as long as they are conducted within 4 weeks of the Baseline/Loading Dose Visit on Day 1.

### 7.2.2. Dosing

Eligible participants will report to the study site on Day 1 to complete baseline assessments and reaffirm eligibility. Day 1 should occur no earlier than 28 days after the participant's last dose (i.e., Day 169 [Week 24 Visit]) in Study 233AS101.

Assessments collected at the End of Study Visit (i.e., Day 197 [Week 28 Visit]) or at the Safety Follow Up (Alternative End of Study Visit) (i.e., Day 225 [Week 32 Visit]) of Part C of Study 233AS101 may be used as the Day 1 predose assessments for Study 233AS102 if they are collected within 48 hours of the first dose in Study 233AS102.

On dosing days, participants will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the Investigator and in compliance with the institutional requirements, once the participants have adequately recovered from the dosing procedure. Participants will receive a safety follow-up telephone contact approximately 24 hours after the procedure.

#### 7.2.2.1. Loading Dose Period

The Loading Dose Period of the study will occur from Day 1 to Day 29.

- Participants who have completed Parts A or B of Study 233AS101:
  - Participants will receive 3 loading doses of BIIB067 approximately 2 weeks apart (Day 1, Day 15, and Day 29).
- Participants who have completed Part C of Study 233AS101:
  - Participants randomized to receive placebo during Study 233AS101 will receive 3 loading doses of BIIB067, approximately 2 weeks apart (Day 1, Day 15, and Day 29). The Investigators, study staff (except for an unblinded designated pharmacist/technician), and study participants will be blinded to the study treatment during the Loading Dose Period.
  - Participants randomized to receive BIIB067 during Study 233AS101 will receive 2 loading doses of BIIB067, on Days 1 and 29, and 1 dose of placebo on Day 15. The Investigators, study staff (except for an unblinded designated

pharmacist/technician), and study participants will be blinded to the study treatment during the Loading Dose Period.

#### 7.2.2.2. Maintenance Dose Period

During the maintenance portion of the study, participants will receive up to 90 doses of BIIB067, approximately every 4 weeks, during visits at Weeks 8, 12, and 16 and every 4 weeks thereafter until the last participant enrolled has had the opportunity to have their Week 152 Maintenance Dose Visit.

### 7.2.3. Follow-Up

Participants will return for their final visit, which will be 4 weeks after their last dose. Participants who withdraw from the study early will return for an Early Termination Visit, which will be 4 weeks after their last dose.

## 7.3. Study Stopping Rules

The Sponsor may terminate this study at any time, after informing Investigators. The Sponsor will notify Investigators if the study is to be placed on hold, completed, or terminated.

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

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

## 7.4. End of Study

The end of study is last participant, last visit (approximately 4 weeks after their last dose). The last Maintenance Dose Visit for a participant will occur when the last participant enrolled has had the opportunity to have their Week 152 Maintenance Dose Visit.

# 8. SELECTION OF PARTICIPANTS

## 8.1. Inclusion Criteria

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

1. Ability of the participant to understand the purpose and risks of the study and indicate consent, and ability of the participant or his/her legally authorized representative to provide signed and dated informed consent and authorization to use PHI in accordance with national and local participant privacy regulations.

2. Must have diagnosis of SOD1-ALS and must have completed the End of Study Visit for either Parts A, B, or C of Study 233AS101 (i.e., were not withdrawn).

3. If taking riluzole, participant must be receiving a stable dose for ≥ 30 days prior to Day 1.

4. If taking edaravone, participant must have initiated edaravone ≥ 60 days (2 treatment cycles) prior to Day 1. Edaravone may not be administered on dosing days during this study.

5. Medically able to undergo the study procedures, and to adhere to the visit schedule at the time of study entry, as determined by the Investigator.

6. Must have screening values of coagulation parameters including platelet count, INR, PT, and aPTT within normal ranges. Coagulation tests may be repeated at the local laboratory once if, in the opinion of the Investigator, values of the initial tests are out of range but deemed not clinically significant. Participants with nonclinically significant and stable out-of-range values may be eligible to enroll in the study at the discretion of the Investigator. (For normal ranges, please refer to the Study Reference Guide).

7. Female participants of childbearing potential must agree to practice effective contraception during the study and be willing and able to continue contraception for 5 months after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to (see Section 15.5).

8. Participants in Parts A and B must have a washout ≥ 16 weeks between the last dose of study treatment received in Study 233AS101 and the first dose of BIIB067 received in the current Study 233AS102. Participants in Part C do not require a washout period.

## 8.2. Exclusion Criteria

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

Medical History

1. History of drug abuse or alcoholism within 6 months before study enrollment that would limit participation in the study, as determined by the Investigator.

2. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy, or any other ongoing medical condition during the screening period that, according to the Investigator, would interfere with the conduct or assessments of the study.

3. Significant cognitive impairment, clinical dementia, or unstable psychiatric illness, including psychosis, suicidal ideation, suicide attempt, or untreated major depression ≤90 days, as determined by the Investigator.

4. History of allergies to a broad range of anesthetics.

5. Presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that is not managed optimally and could place a participant at an increased risk for bleeding during or after an LP procedure. These risks could include, but are not limited to, anatomical factors at or near the LP site (e.g., vascular abnormalities, neoplasms, or other abnormalities) and underlying disorders of the coagulation cascade, platelet function, or platelet count (e.g., hemophilia, Von Willebrand's disease, liver disease).

6. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter.

7. Clinically significant abnormalities in hematology or clinical chemistry parameters, as determined by the Investigator, which would render the participant unsuitable for enrollment.

8. Clinically significant, as determined by the Investigator, 12-lead ECG abnormalities, including corrected QT interval using Fridericia's correction method of > 450 ms for males and > 470 ms for females.

Medications

9. Prior or current treatment with small interfering RNA, stem cell therapy, or gene therapy.

10. Treatment with another investigational drug, biological agent (excluding BIIB067), or device within 1 month or 5 half-lives of study agent, whichever is longer.

11. Current or anticipated need, in the opinion of the Investigator, of a DPS during the study period.

12. Current or recent (within 1 month) use, or anticipated need, in the opinion of the Investigator, of copper (II) (diacetyl-bis[N4-methylthiosemicarbazone]) or pyrimethamine.

13. Anticipated need, in the opinion of the Investigator, for administration of any antiplatelet or anticoagulant medication that cannot be safely continued or held for an LP procedure, if necessary, according to local or institutional guidelines and/or Investigator determination.

Other

14. Female participants who are pregnant or currently breastfeeding.

15. Current enrollment in any other interventional study.

16. Inability to comply with study requirements.

17. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the participant unsuitable for enrollment.

# 9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

## 9.1. Screening and Enrollment

Participants (or their legally authorized representative [e.g., spouse], where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). When a participant signs the ICF, that participant is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a participant is excluded from the study, the reasons for exclusion will be documented in the participant's source documents and on the screening log.

Participants who fail screening can be rescreened once at the discretion of the Investigator. All rescreening must be completed within 56 calendar days after the start of the screening period (Study 233AS101 Day 169 [Week 24 Visit]).

## 9.2. Randomization and Registration of Participants

Participants will be registered on Day 1 after all predose assessments have been completed, and after the Investigator has verified that the participants are eligible per criteria in Sections 8.1 and 8.2. No participant may begin treatment before being assigned a unique identification number. Participant identification numbers that are assigned will not be reused, even if the participant does not receive treatment. Participants will not be randomized.

Refer to the Study Reference Guide for details on registration.

## 9.3. Blinding Procedures

This is an open-label, long-term extension study of BIIB067 in participants with SOD1-ALS who have completed either Parts A, B, or C of Study 233AS101. In Study 233AS101, the Investigators, study staff (except for an unblinded designated pharmacist/technician), and study participants are blinded to the randomized study treatment assignments. To preserve the blinding used in Study 233AS101 until database lock, participants who completed Parts A or B of Study 233AS101 will have a washout period of at least 4 times the $t_{½}$ (~16 weeks) from the time of their last dose of study treatment in Study 233AS101 to their first dose in Study 233AS102. Participants who completed Part C of Study 233AS101 will have a blinded Loading Dose Period (see Section 7.2.2.1 for details).

# 10. DISCONTINUATION OF STUDY TREATMENT OR WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

## 10.1. Discontinuation of Study Treatment

A participant must discontinue study treatment for any of the following reasons:

- The participant becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The participant withdraws consent to continue study treatment.
- The participant experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The participant is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

The reason for discontinuation of study treatment must be recorded in the participant's CRF.

Participants who discontinue study treatment will be encouraged to remain in the study and complete all applicable protocol-specified tests and assessments. In circumstances when onsite visits are not possible, these assessments may be conducted by telephone.

Participants who terminate from the study early (i.e., discontinue both study treatment and study assessments) should complete the Final or Early Termination Visit. Home assessments will be allowed with Investigator approval for participants who are unable to complete the Final or Early Termination Visit at the site.

## 10.2. Withdrawal of Participants From Study

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

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

The reason for the participant's withdrawal from the study must be recorded in the participant's CRF.

# 11. STUDY TREATMENT USE

## 11.1. Regimen

### 11.1.1. Participants Who Have Completed Parts A or B of Study 233AS101

Participants will receive 3 loading doses of BIIB067, approximately 2 weeks apart, during the first 4 weeks, and up to 90 maintenance doses of BIIB067, approximately every 4 weeks, by IT injection.

All participants who were not receiving the 100 mg dose of BIIB067 will be dosed at BIIB067 100 mg at their next scheduled Maintenance Dose Visit.

### 11.1.2. Participants Who Have Completed Part C of Study 233AS101

Participants will not have a washout period. Participants who received placebo while in Part C of Study 233AS101 will receive 3 loading doses of BIIB067 100 mg approximately once every 2 weeks (Days 1, 15, and 29), while participants who received BIIB067 in Part C of Study 233AS101 will receive 2 doses of BIIB067 100 mg, on Days 1 and 29, and placebo on Day 15. All participants will receive BIIB067 100 mg at each Maintenance Dose Visit (up to 58 doses) thereafter. Study treatment administered to participants during the Loading Dose Period is to be blinded.

### 11.1.3. All Participants

Prior to injection, approximately 10 mL of CSF will be collected for analyses. Depending on institutional guidelines, anesthesia or sedation may be used for the LP procedure. On dosing days, participants will remain at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the Investigator and in compliance with the institutional requirements, once the participants have adequately recovered from the dosing procedure. Participants will receive a safety follow-up telephone contact approximately 24 hours after the procedure. During the follow-up periods, participants will remain under observation in the clinic for approximately 1 hour after the LP procedure and will receive a safety follow-up telephone contact approximately 24 hours after the procedure. Refer to and follow the DHA.

## 11.2. Modification of Dose and/or Treatment Schedule

The dosage should not be modified, other than as stated in Section 7.2.2. Any change in the planned dose or dosing regimen would require a protocol amendment.

## 11.3. Concomitant Therapy and Procedures

### 11.3.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between Day 1 and the Final or Early Termination Visit.

#### 11.3.1.1. Allowed Concomitant Therapy

Participants taking concomitant riluzole at study entry must be receiving a stable dose for ≥30 days prior to the first dose of study treatment (Day 1). These participants should remain on this stable dose of riluzole until the completion of the Week 12 Visit, unless riluzole use must be discontinued in the judgment of the Investigator, in which case it should not be restarted until the completion of the Week 12 Visit. If participants are not receiving riluzole at Day 1, they should not initiate it until the completion of the Week 12 Visit.

Participants taking concomitant edaravone at study entry must have initiated edaravone ≥60 days (2 treatment cycles) prior to the first dose of study treatment (Day 1). Edaravone may not be administered on dosing days of this study. These participants should remain on this stable dose of edaravone until the completion of the Week 12 Visit, unless edaravone use must be discontinued in the judgment of the Investigator, in which case it should not be restarted until the completion of the Week 12 Visit. If participants are not receiving edaravone at Day 1, they should not initiate it until the completion of the Week 12 Visit.

Concomitant medication for symptom management during the study is at the discretion of the Investigator. Participants with questions about allowed concomitant therapy should seek medical guidance from the Investigator.

#### 11.3.1.2. Disallowed Concomitant Therapy

Any antiplatelet or anticoagulant medication that cannot be safely continued or held for an LP procedure, if necessary, according to local or institutional guidelines and/or Investigator determination is prohibited for the duration of the study.

Use of DPS, copper (II) (diacetyl-bis[N4-methylthiosemicarbazone]), or pyrimethamine is prohibited for the duration of the study.

Treatment with small interfering RNA, stem cell therapy, or gene therapy is prohibited.

Off-label use of any disease-modifying treatment for ALS is prohibited for the duration of the study.

Participants should be instructed to contact their Investigator before taking any new medications, including nonprescription drugs and herbal preparations.

### 11.3.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the participant is enrolled in the study and the final study visit.

## 11.4. Continuation of Treatment

There is no provision to provide study treatment after the study.

# 12. STUDY TREATMENT MANAGEMENT

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA aligns with all other references, including the protocol.

Study treatment must be dispensed only by a Pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once study treatment is prepared for a participant, it can be administered only to that participant. Study treatments are for one-time use only; do not use any study treatment remaining in the vial for another participant.

## 12.1. BIIB067

The Sponsor will supply BIIB067 as a liquid in vials containing approximately 16.4 mL per vial, to ensure 15.0 mL deliverable volume after withdrawal from vial and dose preparation. The drug product is a sterile, parenteral solution formulation that contains BIIB067 drug product 6.7 mg/mL, sodium dihydrogen phosphate dihydrate [redacted] mg/mL, sodium phosphate dibasic anhydrous [redacted] mg/mL, sodium chloride [redacted] mg/mL, potassium chloride [redacted] mg/mL, calcium chloride dihydrate [redacted] mg/mL, and magnesium chloride hexahydrate in water for injection [redacted] mg/mL, pH 7.2.

The contents of the BIIB067 label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. The expiry or use-by date will be stored in the IRT system, and printable assignment reports will be available to site personnel. BIIB067 should not be used after the expiration date.

### 12.1.1. BIIB067 Preparation

The individual preparing BIIB067 should carefully review the instructions provided in the DHA.

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

### 12.1.2. BIIB067 Storage

Study treatment must be stored in a secure location.

BIIB067 is to be protected from light and stored at 2°C to 8°C (36°F to 46°F), in a monitored, locked refrigerator, with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

### 12.1.3. BIIB067 Handling and Disposal

The Investigator must return all used and unused vials of BIIB067 as instructed by the Sponsor, unless approved for onsite destruction.

If any BIIB067 supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from the Sponsor, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

### 12.1.4. BIIB067 Accountability

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

Unless otherwise notified, the study site must save all vials, both used and unused, for study treatment accountability. At the end of the study, reconciliation must be made between the amount of BIIB067 supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation must be provided for any discrepancies.

## 12.2. Placebo Product

Placebo is to be stored at 2°C to 8°C (36°F to 46°F), in a monitored, locked cabinet with limited access.

The Sponsor manufactures the matching placebo (artificial CSF), supplied as a liquid in vials containing approximately 21 mL per vial for use during the blinded Loading Dose Period in participants who enrolled after completing Part C of Study 233AS101. The drug supply label will include conditions for storage, lot number, and other pertinent information.

# 13. CLINICAL FUNCTION, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

See Section 4 for the timing of assessments.

## 13.1. Clinical Function Assessments

The following clinical assessments will be performed to evaluate the clinical function of BIIB067. See Section 4 for the timing of assessments. All study visits are expected to occur at the site, unless the participant is unable to travel to the site; then, a home visit may be possible at the discretion of the Investigator.

### 13.1.1. ALS Functional Rating Scale-Revised

The ALSFRS-R has been demonstrated to predict survival. The ALSFRS-R measures 4 functional domains, including respiratory, bulbar function, gross motor skills, and fine motor skills. There are 12 questions, each scored from 0 to 4, for a total possible score of 48, with higher scores representing better function [Cedarbaum 1999]. At each study site, the same qualified and trained study site staff member will consistently perform the ALSFRS-R for a participant. A qualified and trained backup ALSFRS-R rater will be identified in case the primary rater is unavailable.

In order to maintain the blinded treatment in Study 233AS101, study site staff that are trained, qualified, and designated to perform the ALSFRS-R assessment will remain blinded to other study procedures in Study 233AS102 until the end of the blinded Loading Dose Period.

### 13.1.2. Slow Vital Capacity

Vital capacity will be measured by means of an SVC test, administered in the upright position. The procedure will be performed according to the study Pulmonary Procedure Manual. Upright SVC will be determined by performing 3 to 5 measures, in accordance with criteria established by the American Thoracic Society and the European Respiratory Society [Miller 2005; Pellegrino 2005; Wanger 2005]. The results will be overread by a central reader to confirm that these criteria (at least 3 acceptable tests with the 2 highest acceptable [largest and next largest] efforts within 150 mL of vital capacity) have been achieved.

### 13.1.3. Participant Diary

At Screening, participants will be given diaries to record the date and time of ventilation use. This diary will be reviewed with study site staff at each visit. Refer to the Study Reference Guide for details.

[redacted]

[redacted]

### 13.1.5. Handheld Dynamometry

Muscle strength is an important determinant of both function and ultimate survival in ALS. Quantitative muscle strength will be evaluated using the HHD Megascore, which tests isometric strength of multiple muscles using standard participant positioning. Approximately 8 muscle groups will be examined (per each side) in both upper and lower extremities.

[redacted]

[redacted]

## 13.2. Pharmacokinetic Assessments

BIIB067 concentrations in plasma and CSF will be determined using validated assays.

Samples for analysis of BIIB067 concentrations in plasma and CSF will be collected from each participant at the timepoints specified in Section 4.

## 13.3. Pharmacodynamic/Biomarker Assessments

The following tests may be performed to assess the PD properties of BIIB067. Refer to Section 4 for the timing of assessments.

- [redacted], plasma, [redacted] samples will be collected to assess the modulation of potential PD assessments and other biomarkers that may be related to

BIIB067 activity or ALS disease activity. [redacted]

- [redacted]
- The biomarkers to be analyzed may include, but are not limited to, the following:
  - Total SOD1 protein in CSF
  - [redacted]
  - [redacted]
  - NfL in [redacted] and plasma
  - [redacted]

[redacted]

## 13.4. Genomic and Pharmacogenomic Assessments

For participants who did not have the presence or absence of a SOD1 mutation confirmed centrally in Study 233AS101, a one-time blood sample will be collected. For participants who did not have a blood sample collected for testing of other genes related to ALS and/or the response to BIIB067 in Study 233AS101, an additional blood sample will be collected. The main ICF will govern use of these samples in genetic analyses to understand ALS and the response to BIIB067 in the context of this clinical program.

In addition, where not prohibited by regulatory authorities or ethics committees, an optional genetic consent will be offered to these participants to allow samples to be stored for future unspecified genetic research related to other diseases and traits of interest to the Sponsor.

Approximately 10% of ALS is known to be caused by genetic mutations; to date, at least 20 genes have been identified as causative of or highly associated with ALS, including SOD1. The DNA sample will be analyzed for genetic variation in the SOD1 gene to determine the spectrum of likely pathogenic mutations in the gene and to assess if SOD1 polymorphisms affect response to treatment. In addition, samples collected during the study may be analyzed for genetic variation in other genes of known and probable relevance for the pathogenesis of ALS and neurodegeneration, including but not limited to TAR DNA-binding protein, fused in sarcoma, chromosome 9 open reading frame 72, optineurin, valosin-containing protein, ubiquilin 2, profilin 1, and ataxin.

In the event of an unusual response or observation of unexplained AEs, DNA samples may be used to determine if there are any pharmacogenomics associations with drug response.

In the future, as the understanding of ALS and BIIB067 increases, additional genomic analyses may be warranted to refine the knowledge of the molecular basis of the disease and the drug response as well as to advance the development of novel therapeutics. The sample will only be used in genetic analyses to understand ALS, neurodegeneration, and response to BIIB067.

The DNA samples will be coded with the participant's identification number and may be stored for up to 25 years after the end of the main study or a duration dictated by local, national, or regional laws or regulations. No genotyping or genomic data will be provided back to the participant. Participants may withdraw consent and request to have their samples destroyed at any time, and no further genetic data will be generated; any data already generated will not be destroyed.

# 14. SAFETY ASSESSMENTS

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

## 14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BIIB067:

- Medical history
- Physical examinations
- Limited neurological examinations (to be assessed by a trained specialist) of coordination/cerebellar function, reflexes, and motor system
- Vital sign measurements: temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate will be measured after the participant has rested in a sitting position for at least 5 minutes
- Weight measurements
- 12-lead ECGs (paper; as applicable)
- C-SSRS
- Concomitant therapy and procedure recording
- AE and SAE recording

## 14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of BIIB067:

- Hematology: Complete blood count with differential and platelet count. Platelet count will also be measured for all participants at Screening and at all dosing and final/early termination visits
- Coagulation: INR, PT, and aPTT (all of which will also be measured for all participants at Screening and at all dosing and final/early termination visits)
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium

- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal)
- Pregnancy tests
- CSF: red and white blood cell count, protein, and glucose

The majority of clinical laboratory samples will be collected at the clinic and analyzed by a central laboratory external to the clinic. Pregnancy tests will be collected and analyzed at the clinic. CSF will be collected in the clinic and analyzed at the local laboratory. At each CSF collection, 2 sample tubes will be sent to the local laboratories for routine cell count, differential count, and for protein and glucose analysis. In addition, should repeat coagulation or hematology tests be required, these may be collected in the clinic and sent to the local laboratory for analysis to facilitate timely review.

## 14.3. Product-Specific Safety Assessments

If performed, anti-BIIB067 antibody assessments will be performed according to the schedule provided in Section 4.

# 15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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

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

## 15.1. Definitions

### 15.1.1. Adverse Event

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

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the participant to receive specific corrective therapy
- A laboratory abnormality that the Investigator considers to be clinically significant

### 15.1.2. Serious Adverse Event

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

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

- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important event

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

### 15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment, including hospitalization that is part of the study design (e.g., admission to the clinic for the purposes of dosing or post-LP observation) will not be considered an SAE, even if the participant 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 participant'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 participant'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 participant is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

## 15.2. Safety Classifications

### 15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

### 15.2.2. Relationship of Events to Study Treatment and Lumbar Puncture

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

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

| Relationship of Event to Lumbar Puncture | |
|---|---|
| Not related | An AE will be considered "not related" to the LP procedure if there is not a reasonable possibility that the event has been caused by the LP procedure. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between the LP procedure and the event, the presence of a biologically implausible relationship between the LP procedure and the AE, or the presence of a more likely alternative explanation for the AE. |
| Related | An AE will be considered "related" to the LP procedure if there is a reasonable possibility that the event may have been caused by the LP procedure. Factors that point toward this assessment include but are not limited to: a reasonable temporal sequence between the LP procedure and the event, a known response pattern of the LP procedure (e.g., bleeding from the puncture site), a biologically plausible relationship between the LP procedure and the AE, or a lack of an alternative explanation for the AE. |

### 15.2.3. Severity of Events

The severity of AEs and SAEs will be graded using the National Cancer Institute CTCAE (version 4). Any AE not listed in the CTCAE will be graded as follows:

| Severity of Event | |
|---|---|
| Grade | Definition |
| 1 | Mild AE |
| 2 | Moderate AE |
| 3 | Severe or medically significant AE |
| 4 | Life-threatening AE |
| 5 | Death related to AE |

### 15.2.4. Expectedness of Events

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

## 15.3. Monitoring and Recording Events

### 15.3.1. Adverse Events

Any AE experienced by the participant between the time of first dose of study treatment and the last study visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, post-LP telephone contact, and the Final or Early Termination Visit, the Investigator will assess the participant for AEs and will record any new AEs or updates to previously reported AEs on the CRF.

AEs that are ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will not be recorded on the CRF.

### 15.3.2. Serious Adverse Events

Any SAE experienced by the participant between the time of the signing of the ICF and the final study visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the Sponsor within 24 hours or according to national law as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported with 24 hours.

Participants will be followed for all SAEs until the final study visit. Thereafter, the event should be reported to the Sponsor only if the Investigator considers the SAE to be related to study treatment.

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

### 15.3.3. Immediate Reporting of Serious Adverse Events

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

| **Reporting Information for SAEs** |
|---|
| A report ***must be submitted*** to the Sponsor regardless of the following:<br>• Whether or not the participant has undergone study-related procedures<br>• Whether or not the participant has received study treatment<br>• The severity of the event<br>• The relationship of the event to study treatment<br>To report initial or follow-up information on an SAE, fax a completed SAE form; refer to the Study Reference Guide for complete contact information. |

#### 15.3.3.1. Deaths

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

### 15.3.4. Suspected Unexpected Serious Adverse Reactions

SUSARs are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

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

The Sponsor will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

## 15.4. Procedures for Handling Special Situations

### 15.4.1. Pregnancy

**Participants should not become pregnant during the study and for 5 months after their last dose of study treatment.** If a female participant becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female participant by faxing or emailing the appropriate form to the Sponsor within 24 hours of the study site staff becoming aware of the pregnancy; refer to the Study Reference Guide for complete contact information. The Investigator or study site staff must report the outcome of the pregnancy to the Sponsor. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

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

### 15.4.2. Overdose

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

### 15.4.3. Medical Emergency

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

#### 15.4.3.1. Unblinding for Medical Emergency

In a medical emergency during the Loading Dose Period, when knowledge of the participant's study treatment assignment may influence the participant's clinical care, the Investigator and, if applicable, designated site personnel at the Sponsor, may access the participant's study treatment assignment by IRT. The Investigator must document the reasons for unblinding in the participant's source documents. The Investigator is strongly advised not to divulge the participant's study treatment assignment to any individuals who are not directly involved in managing the medical emergency or to site personnel who are involved with the analysis and conduct of the study. The Investigator can contact the Sponsor or designee to discuss such situations.

## 15.5. Contraception Requirements

All women of childbearing potential must ensure that effective contraception is used during the study and for 5 months, whichever is longer, after their last dose of study treatment. In addition, female participants should not donate eggs for the duration of the study and for at least 5 months after their last dose of study treatment.

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

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

For the purposes of the study, effective contraception is defined as use of at least 1 of the following:

For females:

- Established use of oral, injected, implanted, intravaginal, or transdermal hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).
- True abstinence, when this is consistent with the preferred and usual lifestyle of the participant, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

## 15.6. Safety Responsibilities

### 15.6.1. The Investigator

The Investigator's responsibilities include the following:

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

### 15.6.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before study site activation and participant enrollment, the Clinical Monitor is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- The Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

# 16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

## 16.1. Analysis Population

The safety population is defined as participants who enrolled and have received at least 1 dose of study treatment in the extension study. The analyses of clinical function and safety for 233AS102 will be performed for the safety population. Integrated analyses of 233AS101 and 233AS102 will be performed for the populations defined in 233AS101 protocol for mITT and non-mITT.

For participants from Part C of 233AS101 who enrolled in 233AS102, summaries for clinical function, PK, PD/biomarker endpoints, and safety evaluations will also be presented by disease progression subgroup (i.e., those who met prognostic enrichment criteria for rapid disease progression in 233AS101 Part C [labelled as "enriched" for analyses] and all other eligible participants in 233AS101 Part C [labelled as "other"]). Summaries of data collected during 233AS102 for participants from Part C of 233AS101 will be presented by prior treatment group from 233AS101. Integrated summaries of 233AS101 and 233AS102 will be presented by treatment group during 233AS101 for each of the mITT and non-mITT populations, with some limited summaries for overall intention-to-treat population.

Generally, data for participants from 233AS101 Part C will be analyzed separately from that of participants from Parts A and B, but there may be some analyses where all participants in the extension study will be pooled, particularly for safety summaries. Participants from Parts A and B will generally be pooled together; the data in these participants will mainly be grouped overall rather than by dose level, but there may be limited summaries based on individual dose level. Further details will be provided in the interim and/or final statistical analysis plan.

Some of the analyses specified will be more relevant for integrated efficacy, safety, and immunogenicity plans where data from both 233AS101 and 233AS102 will be pooled.

## 16.2. Clinical Function

### 16.2.1. Methods of Analysis

As this is an open-label, long-term extension study, analyses will be exploratory and descriptive in nature.

Data will be summarized using descriptive statistics for continuous variables and using frequency and percentage for discrete variables. For participants who have completed Parts A or B of Study 233AS101, the time trajectory of each clinical function may be summarized at selected timepoints and presented in plots. For participants who have completed Part C of Study 233AS101, the time trajectory will be summarized by the prespecified subgroup (enriched population versus other eligible participants) and the prior treatment received during Study

233AS101 from the baseline of Study 233AS101 (including data from Studies 233AS101 and 233AS102), from the baseline of Study 233AS102 (including data from Study 233AS102 only), and from the start of BIIB067 100 mg dosing.

Efficacy will be measured based on changes in ALSFRS-R, percent predicted SVC, HHD Megascore and individual muscle strength, [redacted]. Changes from baseline (using definitions outlined above) will be summarized over time for each of these endpoints.

Analysis of covariance using multiple imputation will be performed at selected timepoints, based on level of data available at interim and final analysis.

Time to death or permanent ventilation (i.e., ≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days) and time to death will be summarized using Kaplan-Meier curves based on the starting time using the following:

1. Entry into Study 233AS101
2. Entry into Study 233AS102
3. The start of BIIB067 100 mg dosing
4. Time of symptom onset

The relationship between PK or PD endpoints and the clinical function endpoints will also be explored.

## 16.3. Pharmacokinetics

### 16.3.1. Analysis Population

The PK population is defined as participants who have received at least 1 dose of study treatment and have at least 1 available postdosing evaluation of PK endpoints in the extension study.

### 16.3.2. Methods of Analysis

Plasma and CSF BIIB067 concentrations will be summarized using descriptive statistics and, where warranted, presented graphically.

## 16.4. Pharmacodynamics

### 16.4.1. Analysis Population

The PD population is defined as participants who have received at least 1 dose of study treatment and have at least 1 available postdosing evaluation of the respective PD endpoint in the extension study.

### 16.4.2. Methods of Analysis

The PD/biomarker endpoints will be analyzed using similar methods to those used for clinical functions described above in Section 16.2.1. The relationship between PD/biomarker endpoints and clinical functions will be explored using modeling.

[redacted]

## 16.6. Safety

### 16.6.1. Analysis Population

The safety population is defined as all participants who receive at least 1 dose of study treatment in the extension study.

### 16.6.2. Methods of Analysis

#### 16.6.2.1. Adverse Events

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

The incidence of all AEs, SAEs, deaths (all causes and ALS-related), and AEs leading to discontinuation will be summarized by system organ class and preferred term by treatment group. The incidence rate per person year may also be determined when long-term dosing follow-up is accrued. The AEs level of severity and relationship to study treatment will also be similarly summarized. For the summary of AEs by severity, if a participant has multiple events occurring in the same body system, then the event with the highest severity will be counted. The relationship to study treatment will be classified as related or not related.

#### 16.6.2.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology, coagulation, blood chemistry, CSF assessments, and urinalysis. Laboratory data will be summarized using shift tables. The number and percentage of participants with shifts from baseline to high or low status for hematology, coagulation, blood chemistry, and CSF assessments and shifts from baseline to high or positive status for urinalysis will be presented by treatment group. In addition, summaries of the shift from baseline to the maximum postbaseline value and the shift from baseline to the minimum postbaseline value will be presented.

#### 16.6.2.3. Vital Signs

Changes from baseline will be summarized for all vital signs by visit. A separate summary will be presented for incidence of clinically significant changes from baseline.

#### 16.6.2.4. Columbia Suicide Severity Rating Scale

C-SSRS data will be listed and summarized using descriptive statistics.

#### 16.6.2.5. Limited Neurological Examinations

The changes from baseline in the limited neurological examination (coordination/cerebellar function, reflexes, and motor system) will be summarized by visit.

#### 16.6.2.6. Electrocardiogram

The changes from baseline will be summarized using shift tables. The number and percentage of participants with shifts to the categorical values (abnormal, not AE; or abnormal and AE) will also be summarized.

#### 16.6.2.7. Antigenicity/Immunogenicity

Anti-BIIB067 antibody results will be summarized by prior treatment groups for participants from 233AS101 Part C and will also be summarized for participants from 233AS101 Parts A and B.

## 16.7. Interim Analyses

Interim analyses may be performed periodically to provide content for regulatory submissions and safety updates and to support drug development planning and business activities.

## 16.8. Sample Size Considerations

The sample size for this study is based on the number of the SOD1-ALS participants in Study 233AS101 who consent to participate. Up to 183 participants will be dosed in Study 233AS101.

# 17. ETHICAL REQUIREMENTS

The Sponsor and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable ICH and GCP guidelines and conduct the study according to local regulations.

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

## 17.1. Declaration of Helsinki

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

## 17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor will submit documents on behalf of the investigational sites.

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

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 the Sponsor.

## 17.3. Participant Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the participant or participant's legally authorized representative (e.g., spouse), 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 participant must be explained to the participant (or the participant's legally authorized representative). The participant must be given sufficient time to consider whether to participate in the study.

Participants will be informed that their race and ethnicity will not be collected for the purposes of data analysis during the extension study. However, this information was collected in Study 233AS101, where applicable and after participant consent, unless the collection was not permitted by applicable law or not approved by the governing ethics committee, and the data will be used during analysis of the results of that study.

A copy of the signed and dated ICF must be given to the participant or the participant's legally authorized representative. 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 participant's medical record.

## 17.4. Participant Data Protection

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

During the study, participants' race and ethnicity will not be collected for the purposes of data analysis.

Study reports will be used for research purposes only. The participant will not be identified by name in CRFs, study-related forms, study reports, or any related publications. The Sponsor, 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 participant's personal medical data confidential.

## 17.5. Compensation for Injury

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

## 17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor or partnering companies) with the participant before the participant makes a decision to participate in the study.

## 17.7. Registration of Study and Disclosure of Study Results

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

# 18. ADMINISTRATIVE PROCEDURES

## 18.1. Study Site Initiation

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

## 18.2. Quality Assurance

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

## 18.3. Monitoring of the Study

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

The Clinical Monitor will visit the Investigator at regular intervals during the study and after the study has completed, as appropriate. During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Remote evaluation of data (centralized monitoring) and remote verification of source documentation may also be conducted and reported as defined in the Monitoring Plan.

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

## 18.4. Study Funding

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

## 18.5. Publications

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

# 19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

## 19.1. Public Health Emergencies

In the event of a public health emergency that results in site closure, travel restrictions, and/or the study being deprioritized at the site such that clinic visit(s) cannot occur, a protocol deviation would be incurred for any deviation from the protocol-specified visits and assessments, with additional notation that this protocol deviation is due to the public health emergency. If a protocol-specified clinical visit cannot occur because of a public health emergency, the following mitigating options should be pursued, in order of preference (in which the highest preference option that is feasible should be done): 1) transfer to another active study site that is open, 2) home visit, 3) telemedicine visit (e.g., by telephone or web conference), and 4) local laboratory visit. These mitigating options only apply in the setting of a public health emergency in which a protocol-specified clinic visit cannot occur and should not be pursued solely because of a participant's preference. If the participant does not participate in one of these options, a Safety Telephone call must be conducted within 14 days of the last dosing visit.

A third-party vendor has been engaged to perform the following assessments at the study participant's home:

- Limited neurological examination
- Physical examination
- Vital signs
- Height and body weight collection
- Health outcome measures
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - C-SSRS
  - [redacted]
  - [redacted]

- SVC
- Biological sample collection
- Pregnancy test (if applicable)
- HHD
- Collection/shipment of ventilation diary records

The following assessments will be performed via telephone (telemedicine) by the site staff:

- ALSFRS-R
- [redacted]
- Assessing changes in signs and symptoms as well as review of concomitant medications and AEs

## 19.2. External Contract Organizations

### 19.2.1. Contract Research Organization

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

### 19.2.2. Interactive Response Technology

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

### 19.2.3. Electronic Data Capture

Participant information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool developed and supported by [redacted] and configured by the Sponsor. Ventilation use information will be recorded on paper initially and then via eDiaries developed (as applicable) and supported by [redacted]

### 19.2.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by the Sponsor to analyze all samples collected for the assessment of safety in this study except urine and, where applicable, serum pregnancy tests and CSF, which will be analyzed by a local laboratory; repeat coagulation tests will be analyzed by either the local laboratory or the central laboratory.

## 19.3. Study Committees

### 19.3.1. Independent Data Monitoring Committee

An IDMC will be formed to review ongoing safety and tolerability data. Members of the IDMC will not be allowed to participate as Investigators in this study. The IDMC will review safety data on an ongoing basis to ensure the safe and proper treatment of participants. Regular IDMC meetings will occur approximately every 3 months after the first meeting until the blinded Study 233AS101 is completed. An IDMC charter will provide full guidance on the function and practices to be followed by the IDMC.

## 19.4. 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 participant 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, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a participant. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 17).

## 19.5. Ethics Committee Notification of Study Completion or Termination

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

## 19.6. Retention of Study Data

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

## 19.7. Study Report Signatory

The Sponsor 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 participant enrollment; or by other factors determined to be relevant by the Sponsor.

# 20. REFERENCES

Amyotrophic Lateral Sclerosis Online Genetics Database (ALSoD). 2015.

Andersen PM, Nilsson P, Keränen ML, et al. Phenotypic heterogeneity in motor neuron disease patients with CuZn-superoxide dismutase mutations in Scandinavia. Brain. 1997;120 ( Pt 10):1723-37.

Bruijn LI, Cleveland DW. Mechanisms of selective motor neuron death in ALS: insights from transgenic mouse models of motor neuron disease. Neuropathol Appl Neurobiol. 1996;22(5):373-87.

Bruijn LI, Houseweart MK, Kato S, et al. Aggregation and motor neuron toxicity of an ALS-linked SOD1 mutant independent from wild-type SOD1. Science. 1998;281(5384):1851-4.

Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999;169(1-2):13-21.

Cudkowicz ME, McKenna-Yasek D, Sapp PE, et al. Epidemiology of mutations in superoxide dismutase in amyotrophic lateral sclerosis. Ann Neurol. 1997;41(2):210-21.

Ferlay J, Soerjomataram I, Ervik M. GLOBOCAN 2012 v1.0 Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. International Agency for Research on Cancer. Published 2013 [Accessed 24 Mar 2016]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

Fischer LR, Li Y, Asress SA, et al. Absence of SOD1 leads to oxidative stress in peripheral nerve and causes a progressive distal motor axonopathy. Exp Neurol. 2012;233(1):163-71.

Gurney ME, Pu H, Chiu AY, et al. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. Science. 1994;264(5166):1772-5.

Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review 1975-2012. National Cancer Institute. Published 2015 [Accessed 24 Mar 2016]. Available from: http://seer.cancer.gov/csr/1975_2012/

Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J. 2005;26(1):153-61.

Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev. 2012;3:CD001447.

[redacted]

Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68.

Ratovitski T, Corson LB, Strain J, et al. Variation in the biochemical/biophysical properties of mutant superoxide dismutase 1 enzymes and the rate of disease progression in familial amyotrophic lateral sclerosis kindreds. Hum Mol Genet. 1999;8(8):1451-60.

Reaume AG, Elliott JL, Hoffman EK, et al. Motor neurons in Cu/Zn superoxide dismutase-deficient mice develop normally but exhibit enhanced cell death after axonal injury. Nat Genet. 1996;13(1):43-7.

Smith RA, Miller TM, Yamanaka K, et al. Antisense oligonucleotide therapy for neurodegenerative disease. J Clin Invest. 2006;116(8):2290-6.

Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26(3):511-22.

Writing Group, Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(7):505-512. Epub 2017/05/15.

# 21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

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# AMENDMENT SUMMARY

Biogen Protocol 233AS102

An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation

Version 6

Date: 04 August 2021

EUDRA CT Number: 2016-003225-41

Version 6 of the protocol has been prepared for this amendment, which supersedes Version 5.

## PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 233AS102 is to extend the maintenance dosing portion of the treatment period of the study by up to 124 weeks while minimizing the burden on participants. Maintenance dosing will continue for all participants until the LPI has had the opportunity to reach Week 152 of the maintenance dosing period, which for the first participant in is Week 360. The maintenance dosing period will be followed by a Final Visit at 4 weeks after the last dose. This extends the study until the LPI reaches Week 156. Changes to the study visits include the following:

- The Follow-Up Visits before the Final/Early Termination visit will be eliminated.
- The Final or Early Termination Visit will now be held 4 weeks after the last dose.
- SVC and HHD will be completed every 12 weeks instead of every 4 weeks during the maintenance dosing period.
- ECGs, physical examinations, and limited neurological examinations will be removed from all dosing visits (except for predose at Baseline and as clinically indicated per the discretion of the Investigator). Triplicate ECGs will be reduced to single ECGs.
- The MMSE will be removed as a safety assessment.
- Diary/eDiary use will only be required for days when the participant uses mechanical ventilation.
- Additional days for individual assessments were clarified in the footnotes of the Schedule of Activities table.

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

Section 4, Schedule of Activities for Study 233AS102

*Note: The table and footnotes below have been truncated to only shown rows and columns that are affected by the changes.*

**Now reads:**

| Assessments | Screening Visit[1] | Baseline/1st Loading Dose Visit | | | 2nd Loading Dose Visit | | | 3rd Loading Dose Visit | | | Maintenance Dose Visit | | | ~~Follow-Up Visits~~ | Final or Early Termination Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week -4 to Day -1 | Day 1 | | | Day 15 (±3 days) (Week 2) | | | Day 29 (±3 days) (Week 4) | | | Weeks 8, 12, 16, and every 4 weeks thereafter up to Week ~~236~~ **360** (±3 days) | | | ~~Weeks 240 and 244 (±7 days) (4 and 8 weeks after last dose)~~ | ~~Week 248 (±7 days) or 12~~ **4** weeks after last dose ~~[Early Termination Visit]~~ |
| | | Pre dose | LP | Post dose | Pre dose | LP | Post dose | Pre dose | LP | Post dose | Pre dose | LP | Post dose | | |
| Ventilation Use[4] | X | X | | | X | | | X | | | X | | | ~~X~~ | X |
| ALSFRS-R | | X[5] | | | X[5] | | | X[5] | | | X[5, 6] | | | ~~X~~ | X[5] |
| SVC[7] | | X[5] | | | X[5] | | | X[5] | | | X[5, ~~6~~ **8**] | | | ~~X~~ | X[5] |
| HHD | | X[5] | | | X[5] | | | X[5] | | | X[5, ~~6~~ **8**] | | | ~~X~~ | X[5] |
| [redacted] | | | | | | | | | | | | | | | |
| C-SSRS[12] | | X | | | | | | X | | | X[6] | | | ~~X~~ | X |
| Vital Signs (temperature, blood pressure, pulse rate, respiratory rate) | X | X | | X | X | | X | X | | X | X | | X | ~~X~~ | X |
| 12-lead ECG[13] | X | X | | | | | | ~~X~~ | | | ~~X~~ | | | ~~X~~ | X |

| Assessments | Screening Visit[1] | Baseline/1st Loading Dose Visit | | | 2nd Loading Dose Visit | | | 3rd Loading Dose Visit | | | Maintenance Dose Visit | | | ~~Follow-Up Visits~~ | Final or Early Termination Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week -4 to Day -1 | Day 1 | | | Day 15 (±3 days) (Week 2) | | | Day 29 (±3 days) (Week 4) | | | Weeks 8, 12, 16, and every 4 weeks thereafter up to Week ~~236~~ **360** (±3 days) | | | ~~Weeks 240 and 244 (±7 days) (4 and 8 weeks after last dose)~~ | ~~Week 248 (±7 days) or 12~~ **4** weeks after last dose ~~[Early Termination Visit]~~ |
| | | Pre dose | LP | Post dose | Pre dose | LP | Post dose | Pre dose | LP | Post dose | Pre dose | LP | Post dose | | |
| Physical Examination[14] | X | X | | | ~~X~~ | | | ~~X~~ | | | ~~X~~ | | | ~~X~~ | X |
| Limited Neurological Examination[14] | X | X | | ~~X~~ | ~~X~~ | | ~~X~~ | ~~X~~ | | ~~X~~ | ~~X~~ | | ~~X~~ | ~~X~~ | X |
| ~~MMSE~~ | ~~X~~ | ~~X~~ | | ~~X~~ | | | | | | | ~~X[11]~~ | | ~~X[11]~~ | | ~~X~~ |
| Clinical Laboratory Samples for Hematology, Coagulation, Chemistry, and Urinalysis[3] | X | X | | | X | | | X | | | X | | | ~~X~~ | X |
| [redacted] | | | | | | | | | | | | | | | |
| AE/Concomitant Therapy and Procedures Recording | | ----------X (ongoing)---------- | | | | | | | | | | | | | |
| SAE Recording | ----------X (ongoing)---------- | | | | | | | | | | | | | | |

[4]Participants will use a diary/**eDiary** to record ventilation use. **The diary/eDiary should be completed only for days when the participant uses mechanical ventilation.** This diary will be reviewed with study site staff at each visit. Refer to the Study Reference Guide for details.

[5]May be performed at any time on the day prior to study treatment administration, predose on the day of study treatment administration, or ~~over 2 days at the Follow-up Visits (Weeks 240 and 244) and~~**at the** Final or Early Termination Visit.

[6]To be performed at Week 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, ~~and 236 (i.e., every 4 weeks) Visits only~~ **236, 240, 244, 248, 252, 256, 260, 264, 268, 272, 276, 280, 284, 288, 292, 296, 300, 304, 308, 312, 316, 320, 324, 328, 332, 336, 340, 344, 348, 352, 356, and 360 (i.e., every 4 weeks).**

[8]To be performed at Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, ~~and 228~~ **228, 240, 252, 264, 276, 288, 300, 312, 324, 336, 348, and 360** (i.e., every 12 weeks) Visits only.

[redacted]

[11]To be performed at Week 12, 24, 36, and 48 Visits (i.e., every 12 weeks); Week 72, 96, 120, 144, 168, 192, ~~and 216~~ **216, 240, 264, 288, 312, 336, and 360** Visits (i.e., every 24 weeks)~~; and Week 228 Visit~~.

[13]**ECGs to be done at Screening, Day 1, Final/Early Termination Visit, and as clinically necessary per the discretion of the Investigator throughout the study.** ~~Triplicate 12-lead (paper)~~ ECGs will be obtained after ~~subject~~**participants** have rested in a supine position for at least 10 minutes. ~~The first ECG will be interpreted, and the last 2 ECGs will be checked for consistency and quality.~~

[14]**A physical examination and limited neurological examination will be performed at the specified timepoints (Screening, Day 1, Final/Early Termination Visit). At all other visits, the physical and/or neurological examination may be performed at the Investigator's discretion.** The components of the limited neurological examination are coordination/cerebellar function, reflexes, and motor system.
[18]Blood samples will be collected on every alternate visit at Week 12, 20, 28, 36, ~~44~~, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148, 156, 164, 172, 180, 188, 196, 204, 212, 220, 228, ~~and 236~~ **236, 244, 252, 260, 268, 276, 284, 292, 300, 308, 316, 324, 332, 340, 348, and 356** (i.e., every 8 weeks) Visits only. Blood samples for anti-BIIB067 ~~Ab~~ **antibody** and PK assessments will be collected at the same time.

## Rationale:

*Extension in study duration:*

The extension in study duration is intended to enable generation of longer-term safety and efficacy data and continued access to study drug for study participants through anticipated commercial availability.

*Reduced duration of follow-up after the last dose of study drug:*

With this amendment, all participants will complete maintenance dosing when the LPI has had the opportunity to complete Week 152 of maintenance dosing, before completing their Final Visit at 4 weeks after their last dose. The reduced duration (28-day) of follow-up after the last dose of study drug is supported by data from the Phase 1 single ascending dose and multiple ascending dose portions of Study 233AS101, which incorporated a 3-to-5-month follow-up period after the last dose of study drug. Since no new safety signals were identified during this follow-up period, a 28-day follow-up period after the last dose of study drug will allow for adequate monitoring of study participants.

*Reduced frequency of assessments:*

The frequency of SVC and HHD assessments was reduced to once every 12 weeks during the maintenance dosing period to reduce the burden of efficacy assessments and support participant retention. The requirement to enter ventilation data in the diary/eDiary was refined to only apply to days when ventilation assistance was used to minimize burden for participants in line with Study 233AS101. MMSE assessments were eliminated, and the frequency of the ECG, physical examination, and limited neurological examination was reduced to minimize the burden on participants while still maintaining appropriate safety monitoring. The changes in the frequency of safety assessments reflect the increased understanding of the safety profile of BIIB067based on the totality of data across the program.

This change also affects **Section 7.1**, **Study Overview**; **Section 7.2**, **Overall Study Duration and Follow-Up; Section 7.2.2.2, Maintenance Dose Period; Section 7.2.3, Follow-Up; Section 7.4, End of Study; Section 11.1, Regimen; Section 11.3,**

**Concomitant Therapy and Procedures; Section 14.1, Clinical Safety Assessments; Section 15.3.1, Adverse Events; Section 15.3.2, Serious Adverse Events;** and **Section 16.6.2.5, Limited Neurological Examinations**.

# SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 3, Synopsis

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

Section 4, Schedule of Activities for Study 233AS102

**Change:** The procedures for reviewing coagulation tests and/or platelet counts prior to LP were clarified.**Now reads:**[3]~~Coagulation and/or platelet tests may be repeated at the local laboratory if, in the opinion of the Investigator, values of the initial tests are out of range but deemed not clinically significant. The results of the most recent (i.e., obtained at previous visit) centrally read coagulation tests and platelet count must be reviewed before LP can be performed.~~**The results of the most recent centrally read coagulation tests and platelet count (i.e., those obtained at the previous visit) must be reviewed before LP is performed. Should these results suggest, in the opinion of the Investigator, that LP may be safely performed, then no further review of coagulation tests and platelet counts would be required before performing the LP. However, should repeat coagulation and platelet tests be clinically indicated in the opinion of the Investigator, then these tests may be done locally, to facilitate timely review.**

**Rationale:** This revision was provided to avoid confusion regarding study procedures for reviewing coagulation tests and/or platelet counts prior to LP.

Section 4, Schedule of Activities for Study 233AS102

**Change:** Footnote 7 was revised to clarify the procedures for participants who begin the study not using a facemask but later develop the need to use one.

**Now reads:**[7]If a facemask is used in Study 233AS101 or at screening and/or baseline of this study, it should be used for all SVC assessments for the duration of the study. If a facemask is not used during Study 233AS101 or at screening and/or baseline of this study, it should not be used for the duration of the study**, if possible. If the participant begins the 233AS102 study not using a facemask, but develops the need to use a facemask to complete the SVC during the study, then the facemask should be used for all subsequent SVC assessments for the duration of the study**. Upright SVC will be determined by performing 3 to 5 measures. The results will be overread by a central reader to confirm that these criteria (at least 3 acceptable tests with the 2 highest acceptable [largest and next largest] efforts within 150 mL of vital capacity) have been achieved.

**Rationale:** This change was included to provide flexibility for participants with progressive disease who need to transition to using facemasks for SVC during the study.

Section 5.3.2, Clinical Experience

**Change:** The description of clinical data from Study 233AS101 was expanded.

**Now reads:**

This study is an extension of Study 233AS101, a Phase 1/2/3 study evaluating the benefit/risk of BIIB067. In the single and multiple dose escalation parts (Parts A and B) of this study, BIIB067 at dose levels up to and including 100 mg was generally well tolerated. Most of the AEs were mild or moderate in severity. Plasma concentrations of BIIB067 were dose proportional; CSF concentrations showed a less-than-dose-proportional response. ~~A statistically significant~~ **Administration of BIIB067 100 mg for 12 weeks in Part B of Study 233AS101 led to a 36%** reduction in ~~CSF~~ **total CSF** SOD1 **protein** ~~concentration was~~ **compared to a 3% reduction** observed in the ~~BIIB067 100 mg group (37% reduction) compared with the~~ placebo ~~group (no reduction).~~ [redacted] **Administration** of ~~decline~~ **BIIB067 100 mg for 12 weeks also led to an apparent slowing** in ~~functional (~~**decline across exploratory clinical outcome measures including** ALSFRS-R~~)~~, ~~respiratory (SVC)~~**SVC**, and ~~strength measures (HHD Megascore)~~**HHD Megascore**. ~~These data support the continued development of BIIB067 for the treatment of SOD1-ALS.~~

**Rationale:** This change was included to reflect the final analyses from the multiple ascending dose portion of Study 233AS101.

Section 5.5, Rationale for Dosing Regimen

**Change:** Information on the duration of BIIB067 administration was added.

**Now reads:**

BIIB067 **100 mg** will be administered via IT bolus ~~at 100 mg~~**over 1 to 3 minutes**.

**Rationale:** This change was included to clarify study procedures for how BIIB067 is to be administered.

Section 6.2, Secondary Objectives and Endpoints

**Change:** Consistent with Study 233AS101, the protocol was revised to reflect that plasma NfL will be evaluated as a secondary biomarker endpoint [redacted] The time-to-event endpoints were renamed so that VAFS

was relabeled as time to death or permanent ventilation and so that overall survival was renamed to time to death.**Now reads:**

The secondary objectives are to evaluate the PK, PD, **biomarker effects**, and efficacy of BIIB067 administered to ~~subjects~~**participants** with ALS and a confirmed SOD1 mutation.

6.2.1. Pharmacokinetic Endpoints

The PK endpoints are plasma and CSF levels of BIIB067.

6.2.2. Pharmacodynamic Endpoint~~s~~

The PD endpoint~~s are changes~~ **is the change** from baseline in total ~~CSF~~ SOD1 **protein in CSF** [redacted]

**6.2.3 Biomarker Endpoint**

**The biomarker endpoint is the change from baseline in NfL concentration in plasma.**

~~6.2.3~~**6.2.4.** Efficacy Endpoints

- Efficacy endpoints are changes over time in the following:
  - **Total** ALSFRS-R score~~s~~
  - ~~Slow vital capacity (~~SVC~~)~~
  - ~~Handheld dynamometry (~~HHD~~)~~ Megascore and individual muscle strength
- ~~Ventilation assistance-free survival (VAFS), which is defined as the time to the earliest occurrence of one of the following events:~~**Time to death or permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days)**
  - ~~Death.~~
  - ~~Permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days).~~
- ~~Overall survival~~**Time to death**

**Rationale:** The secondary endpoints were updated to reflect that plasma NfL concentration will be classified as a biomarker endpoint to align with the 233AS101 protocol and to reflect emerging data that neurofilaments are potential biomarkers of ALS disease activity and treatment response. Plasma NfL was selected given the potential utility of a blood-based biomarker in the future, along with assay characteristics. Plasma NfL will be evaluated on the Siemens

Healthineers NfL assay, which has good analytical performance and utilizes a fully automated instrument.

The names of the efficacy endpoints "ventilation assistance-free survival (VAFS)" and "overall survival" were updated to "time to death or permanent ventilation" and "time to death" to more accurately reflect the intended analyses that are being performed for each of these endpoints, and the statistics that will be estimated from the Kaplan-Meier analysis. No change has been made to the intended analysis.

This change also affects **Section 6.3.3, Additional Biomarker Endpoints;** and **Section 13.3, Pharmacodynamic/Biomarker Assessments**.

Section 7.2.2, Dosing

**Change:** References to the last study visit from Part C of Study 233AS101 were updated since either Week 28 or Week 32 Visit could be considered the End of Study Visit.**Now reads:**

Assessments collected at the **End of Study Visit (i.e., Day 197 [Week 28 Visit]) or at the Safety** Follow -Up ~~Visit (4 weeks after last dose)~~**(Alternative End of Study Visit) (i.e., Day 225 [Week 32 Visit])** of Part C of Study 233AS101 ~~will~~**may** be used as the Day 1 predose assessments for Study 233AS102 if they are collected within 48 hours of the first dose in Study 233AS102.

**Rationale:** This change was made to align with updates from the 233AS101 protocol.

This change also affects **Section 7.2.1.2, Participants Who Have Completed Part C of Study 233AS101**.

Section 13.2, Pharmacokinetic Assessments

**Change:** The list of PK parameters for assessment was removed.

**Now reads:**

BIIB067 concentrations in plasma and CSF will be determined using validated assays.

Samples for analysis of BIIB067 concentrations in plasma and CSF will be collected from each participant at the timepoints specified in Section 4.

~~The following PK parameters will be assessed in plasma, when feasible:~~

- ~~Maximum observed concentration~~

- ~~Time to reach the maximum observed concentration~~
- ~~AUC from time 0 to infinity~~
- ~~AUC from time 0 to time of the last measurable concentration~~
- ~~Apparent terminal t½~~

~~The t½ will be assessed in CSF, when feasible.~~

~~Additional PK parameters may be calculated at the discretion of the study Pharmacokineticist.~~

**Rationale:** This change was made to align with the current Schedule of Activities. Blood and CSF samples for PK will only be taken at troughs, so these PK parameters cannot be calculated. This is an error from the previous version.

This change also affects **Section 16.3.2, Methods of Analysis**.

Section 13.4, Genomic and Pharmacogenomic Assessments

**Change:** Details on DNA samples were added to specify that the participant's identification number will be used for coding and the samples may be stored for up to 25 years (or a duration dictated by regulations specific to the location) instead of 15 years.

**Now reads:**

The DNA samples will be coded **with the participant's identification number** and may be stored for up to ~~15~~ **25** years **after the end of the main study or a duration dictated by local, national, or regional laws or regulations**.

**Rationale:** These changes were made to clarify the precautions taken to protect participant privacy as well as reflect Biogen's current standard storage time.

Section 15.3.1, Adverse Events

**Change:** A clarification was added to describe procedures for AEs that are ongoing when the participant completes or discontinues the study.

**AEs that are ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will not be recorded on the CRF.**

**Rationale:** This change was made to reflect current best practices for follow-up of AEs.

Section 15.3.2, Serious Adverse Events

**Change:** A clarification was added to state that SAEs are to be recorded on an SAE form (instead of the CRF) and must be reported to the Sponsor according to national law (in addition to the prespecified timeframe).

**Now reads:**

Any SAE experienced by the ~~subject~~**participant** between the time of the signing of the ICF and the ~~last Follow Up Visit, including the last telephone contact (approximately 24 hours after the Final or Early Termination Visit),~~**final study visit** is to be recorded on ~~the CRF~~**an SAE form**, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to ~~Biogen~~**the Sponsor** within 24 hours **or according to national law** as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported with 24 hours.

~~Subjects~~**Participants** will be followed for all SAEs until the final study visit~~, including the last telephone contact (approximately 24 hours after the Final or Early Termination Visit)~~. Thereafter, the event should be reported to ~~Biogen~~**the Sponsor** only if the Investigator considers the SAE to be related to study treatment.

**Rationale:** This change was made to clarify the safety reporting process and accurately reflect safety reporting requirements.

This change also affects **Section 15.3.3, Immediate Reporting of Serious Adverse Events** and **Section 15.6, Safety Responsibilities**.

Section 15.3.4, Suspected Unexpected Serious Adverse Reactions

**Change:** Guidance text was added regarding unblinding for the purpose of reporting SUSARs.

**Now reads:**

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

**Rationale:** This change was made to reflect the process of unblinding for regulatory reporting purposes.

Section 15.4.3, Medical Emergency

**Change:** Information was included to clarify the procedures for unblinding of a participant's study treatment assignment during a medical emergency.**Now reads:**

### 15.4.3.1. Unblinding for Medical Emergency

**In a medical emergency during the Loading Dose Period, when knowledge of the participant's study treatment assignment may influence the participant's clinical care, the Investigator and, if applicable, designated site personnel at the Sponsor, may access the participant's study treatment assignment by IRT. The Investigator must document the reasons for unblinding in the participant's source documents. The Investigator is strongly advised not to divulge the participant's study treatment assignment to any individuals who are not directly involved in managing the medical emergency or to site personnel who are involved with the analysis and conduct of the study. The Investigator can contact the Sponsor or designee to discuss such situations.**

**Rationale:** This update was made to clarify and expand upon the process of unblinding of site personnel for medical emergencies.

Section 16.1, Analysis Population

**Change:** Details on the analysis population were expanded to include relevant information on the integrated analyses of the 233AS101 and 233AS102 studies, as well as clarification on the subgroup analysis for 233AS102 alone.**Now reads:**

The ~~clinical function~~ **safety** population is defined as ~~subjects~~**participants** who **enrolled and** have received at least 1 dose of study treatment in the extension study. **The analyses of clinical function and safety for 233AS102 will be performed for the safety population. Integrated analyses of 233AS101 and 233AS102 will be performed for the populations defined in 233AS101 protocol for mITT and non-mITT.**

**For participants from Part C of 233AS101 who enrolled in 233AS102, summaries for clinical function, PK, PD/biomarker endpoints, and safety evaluations will also be presented by disease progression subgroup (i.e., those who met prognostic enrichment criteria for rapid disease progression in 233AS101 Part C [labelled as "enriched" for analyses] and all other eligible participants in 233AS101 Part C [labelled as "other"]). Summaries of data collected during 233AS102 for participants from Part C of 233AS101 will be presented by prior treatment group from 233AS101. Integrated summaries of 233AS101 and 233AS102 will be presented by treatment group during 233AS101 for each of the mITT and non-mITT populations, with some limited summaries for overall intention-to-treat population.**

**Generally, data for participants from 233AS101 Part C will be analyzed separately from that of participants from Parts A and B, but there may be some analyses where all participants in the extension study will be pooled, particularly for safety summaries. Participants from Parts A and B will generally be pooled together; the data in these participants will mainly be grouped overall rather than by dose level, but there may be**

**limited summaries based on individual dose level. Further details will be provided in the interim and/or final statistical analysis plan.**

**Some of the analyses specified will be more relevant for integrated efficacy, safety, and immunogenicity plans where data from both 233AS101 and 233AS102 will be pooled.**

**Rationale:** This update was made to reflect analyses described in the 233AS102 and 233AS101/102 integrated statistical analysis plans.

Section 16.2.1, Methods of Analysis

**Change:** The terminology of participant populations for statistical analyses was changed from "fast progressors" and "non-fast progressors" to "enriched population" and "other eligible participants," respectively. Details on the analysis of covariance and Kaplan-Meier curves were clarified.**Now reads:**

Data will be summarized using descriptive statistics for continuous variables and using frequency and percentage for discrete variables. For ~~subjects~~**participants** who have completed Parts A or B of Study 233AS101, the time trajectory of each clinical function may be summarized ~~for the period of each dose level. For~~ **subjectsat selected timepoints and presented in plots. For participants** who have completed Part C of Study 233AS101, the time trajectory will be summarized by the prespecified ~~mutation/progressing group (fast-progressing~~**subgroup (enriched population** versus ~~non-fast progressing~~**other eligible participants**) and the **prior** treatment received during Study 233AS101 from the baseline of Study 233AS101 (including data from Studies 233AS101 and 233AS102), from the baseline of ~~Study 233AS101~~**233AS102** (including data from Study 233AS102 only), and from the start of BIIB067 100 mg dosing.

Efficacy will be measured based on changes in ALSFRS-R, percent predicted SVC, HHD Megascore and individual muscle strength, [redacted]. Changes from baseline (using definitions outlined above) will be summarized over time for each of these endpoints.

~~VAFS~~**Analysis of covariance using multiple imputation will be performed at selected timepoints, based on level of data available at interim** and ~~overall survival~~**final analysis.**

**Time to death or permanent ventilation (i.e., ≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days) and time to death** will be summarized using Kaplan-Meier curves based on the starting time using the following:

1. Entry into Study 233AS101
2. Entry into Study 233AS102
3. The start of BIIB067 100 mg dosing

**4. Time of symptom onset**

**Rationale:** The change in terminology from "fast progressing" and "non-fast progressing" subgroups to "enriched" and "other" populations in the 233AS102 protocol was made to align with language in the 233AS101 protocol. The primary analysis population for Study 233AS101 was enriched, based on SOD1 mutation type and prerandomization ALSFRS-R slope decline, for participants more likely to have rapid disease progression during the study. The terminology used to describe this population in Study 233AS101 was thus changed from "fast progressors" to "participants who met prognostic enrichment criteria for rapid disease progression" to more accurately reflect the population enrolled. Consistently, the terminology for the broader population enrolled (previously "non-fast progressors") was updated to "other eligible participants." No changes have been made to the criteria to define either subgroup.

Multiple imputation for the analysis of covariance will be utilized to increase the robustness of the analysis in the context of varying lengths of follow-up in the extension study. This analysis will also help address problems with missing data due to the COVID-19 pandemic. Other revisions were made to align with the statistical analysis plans.

Section 16.6.2.1, Adverse Events

**Change:** References to “dose level” in the descriptions of analyses were removed and replaced with more general identifiers such as “treatment group” or removed entirely. The summary of the analyses was also revised to reflect the key statistical estimates.

**Now reads:**

The incidence of all AEs, SAEs, deaths (all causes and ALS-related), and AEs leading to discontinuation will be summarized by system organ class and preferred term by ~~time interval on a given dose level~~**treatment group**. The incidence rate per person year may also be determined when long-term dosing follow-up is accrued. ~~Kaplan Meier estimates of survival will also be derived.~~

**Rationale:** These changes were made to more accurately reflect the analyses described in the final statistical analysis plan.

This change also affects **Section 16.6.2.2, Clinical Laboratory Results; Section 16.6.2.3, Vital Signs**; **Section 16.6.2.4, Columbia Suicide Severity Rating Scale**; **Section 16.6.2.5, Limited Neurological Examinations**; **Section 16.6.2.6, Electrocardiogram**; and **Section 16.6.2.7, Antigenicity/Immunogenicity.**Section 18.3, Monitoring of the Study

**Change:** Implemented remote evaluation of data and source documents.

**Now reads:**

The Investigator must permit study-related monitoring by providing direct access to source data and to the ~~subjects' medical histories~~**participants' medical histories**. **Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary**

**(e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.**

The Clinical Monitor will visit the Investigator at regular intervals during the study and after the study has completed, as appropriate. During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

**Remote evaluation of data (centralized monitoring) and remote verification of source documentation may also be conducted and reported as defined in the Monitoring Plan.**

**Rationale:** Remote evaluation of data and source documents is being implemented to allow the Sponsor and CRO to continue to provide oversight of site performance and ensure overall patient safety and data integrity. This process is being implemented because several sites/institutions have restricted on-site access for the CRO monitors during this ongoing COVID-19 pandemic.

Section 19, Further Requirements and General Information

**Change:** Details on contingency plans were added for potential site closure, travel restrictions, or other events resulting from a public health emergency.**Now reads:**

### 19.1 Public Health Emergencies

**In the event of a public health emergency that results in site closure, travel restrictions, and/or the study being deprioritized at the site such that clinic visit(s) cannot occur, a protocol deviation would be incurred for any deviation from the protocol-specified visits and assessments, with additional notation that this protocol deviation is due to the public health emergency. If a protocol-specified clinical visit cannot occur because of a public health emergency, the following mitigating options should be pursued, in order of preference (in which the highest preference option that is feasible should be done): 1) transfer to another active study site that is open, 2) home visit, 3) telemedicine visit (e.g., by telephone or web conference), and 4) local laboratory visit. These mitigating options only apply in the setting of a public health emergency in which a protocol-specified clinic visit cannot occur and should not be pursued solely because of a participant's preference. If the participant does not participate in one of these options, a Safety Telephone call must be conducted within 14 days of the last dosing visit.**

**A third-party vendor has been engaged to perform the following assessments at the study participant's home:**

- **Limited neurological examination**
- **Physical examination**
- **Vital signs**
- **Height and body weight collection**

- **Health outcome measures**
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
    - **C-SSRS**
  - [redacted]
  - [redacted]
- **SVC**
- **Biological sample collection**
- **Pregnancy test (if applicable)**
- **HHD**
- **Collection/shipment of ventilation diary records**

**The following assessments will be performed via telephone (telemedicine) by the site staff:**

- **ALSFRS-R**
- [redacted]
- **Assessing changes in signs and symptoms as well as review of concomitant medications and AEs**

**Rationale:** In the event of a public health emergency, mitigating options provide flexibility with respect to the collection of data in the interest of participant safety and to protect the integrity of the data when participants are unable to attend a clinic visit.

Section 19.3.1, Independent Data Monitoring Committee

**Change:** Added information on the end date for the regular IDMC meetings.**Now reads:**

An ~~independent data monitoring committee (~~IDMC~~)~~ will be formed to review ongoing safety and tolerability data. Members of the IDMC will not be allowed to participate as Investigators in this study. The IDMC will review safety data on an ongoing basis to ensure the safe and proper treatment of ~~subject~~**participants**. Regular IDMC meetings will occur approximately every 3 months after the first meeting **until the blinded Study 233AS101 is completed**. An IDMC charter will provide full guidance on the function and practices to be followed by the IDMC.

**Rationale:** This update was provided for clarification that the IDMC will not continue to meet regularly after the blinded Study 233AS101 has completed.

# SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- Sponsor information was updated.
- References to "SOD1" that refer to the PD endpoint were changed to "total SOD1 protein" for clarity.
- Section 2, List of Abbreviations, was updated.
- Abbreviation format and preferred usage of terms were updated throughout to reflect revisions to the Biogen Style Guide.
- Section 20, References, was updated.
- Typographical errors and formatting were corrected.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALS | amyotrophic lateral sclerosis |
| [redacted] | [redacted] |
| ALSFRS-R | Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised |
| [redacted] | [redacted] |
| COVID-19 | coronavirus disease of 2019 |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| DNA | deoxyribonucleic acid |
| ECG | electrocardiogram |
| [redacted] | [redacted] |
| HHD | handheld dynamometry |
| ICF | Informed consent form |
| IDMC | independent data monitoring committee |
| IRT | interactive response technology |
| LP | lumbar puncture |
| LPI | last participant in |
| mITT | modified intention-to-treat |
| MMSE | Mini-Mental State Examination |
| [redacted] | [redacted] |
| NfL | neurofilament light chain |
| PD | pharmacodynamic(s) |
| [redacted] | [redacted] |
| PK | pharmacokinetic(s) |
| [redacted] | [redacted] |
| SAE | serious adverse event |
| [redacted] | [redacted] |
| SOD1 | superoxide dismutase 1 |
| SOD1-ALS | amyotrophic lateral sclerosis with a confirmed superoxide dismutase 1 mutation |
| SUSAR | suspected unexpected serious adverse reaction |
| SVC | slow vital capacity |
| [redacted] | [redacted] |

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# AMENDMENT SUMMARY

Biogen Protocol 233AS102

An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation

Version 5

Date: 08 November 2019

EUDRA CT Number: 2016-003225-41

Version 5 of the protocol has been prepared for this amendment, which supersedes Version 4.

## PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 233AS102 is to update the secondary [redacted] endpoints, statistical methodology, and sample size. Changes to the secondary [redacted] endpoints include the following:

- Revise the definition of handheld dynamometry (HHD) and ventilation assistance-free survival (VAFS) secondary endpoints
- [redacted]

Statistical methodology was updated to allow the analysis of efficacy using the change from baseline. Sample size was increased from 144 to 183 subjects.

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

Section 6.2.3. Efficacy Endpoints (previously Disease Progression Endpoints)

**Now reads:**

6.2.3. ~~Disease Progression~~ **Efficacy** Endpoints

- ~~Disease progression~~ **Efficacy** endpoints are changes over time in the following:
  - ALSFRS-R scores
  - Slow vital capacity (SVC)
  - Handheld dynamometry (HHD) ~~scores~~ **Megascore and individual muscle strength**
- Ventilation assistance-free survival (VAFS), which is defined as the time to the earliest occurrence of one of the following events:
  - Death.
  - ~~First use of noninvasive~~**Permanent** ventilation (~~NIV) for~~ ≥ 22 hours **of mechanical ventilation [invasive or noninvasive]** per day for ≥ ~~10~~**21** consecutive days**)**.

  - ~~First use of permanent assisted ventilation (PAV) for ≥22 hours per day for ≥7 consecutive days.~~

- Overall survival

[redacted]

[redacted]

Section 16.1.2, Methods of Analysis

**Now reads:**

~~Disease progression~~ **Efficacy** will be measured based on changes in ALSFRS-R, **percent predicted** SVC, HHD **Megascore and individual muscle strength**, [redacted]. **Changes from baseline (using definitions outlined above) will be summarized over time for each of these endpoints.** ~~The linear mixed model for repeated measures (MMRM) will be used to assess the slope of change by mutation/progressing group (fast progressing versus non-fast progressing) and the treatment received during Study 233AS101. Baseline characteristics at the start of Study 233AS101 may be included as fixed covariates. The slope of ALSFRS-R score change will be estimated using linear MMRM as well as derived using data points from each individual participant for each 48-week period. Categorical analysis of slopes in different ordered categories may also be performed.~~

**Rationale:** This was done in alignment with Study 233AS101 to allow integrated analyses of the 233AS101 and 233AS102 studies.

This change also affects Section 13.1.5, Handheld Dynamometry.

Section 16.7, Sample Size Consideration

**Now reads:**

The sample size for this study is based on the number of the SOD1-ALS subjects in Study 233AS101 who consent to participate. Up to ~~144~~ **183** subjects will be dosed in Study 233AS101.

**Rationale:** The sample size was increased due to an increase in sample size for Part C of Study 233AS101 from 60 to 99 subjects who have an opportunity to enroll in this study.

This change also affects Section 7.1, Study Overview.

# SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 3, Synopsis

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

Section 4, Schedule of Activities for Study 233AS102, Table 1

**Change:** The frequency of the [redacted] and Mini-Mental State Examination (MMSE) assessments were reduced. Examination of the cranial nerve was removed as a component of the limited neurological examination. Pregnancy testing was changed to allow testing to be done on either urine or serum.

## Now reads:

| **Assessments** | **Screening Visit[1]** | **Baseline/1st Loading Dose Visit** | | | **2nd Loading Dose Visit** | | | **3rd Loading Dose Visit** | | | **Maintenance Dose Visit** | | | **Follow-Up Visits** | **Final or Early Termination Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Week -4 to Day -1** | **Day 1** | | | **Day 15 (±3 days) (Week 2)** | | | **Day 29 (±3 days) (Week 4)** | | | **Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 236 (±3 days)** | | | **Weeks 240 and 244 (±7 days) (4 and 8 weeks after last dose)** | **Week 248 (±7 days) or 12 weeks after last dose [Early Termination Visit]** |
| | | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | | |
| [redacted] | | | | | | | | | | | | | | | |
| Limited Neurological Examination ~~(including MMSE)~~[12][14] | X | X[10] | | X | X[10] | | X | X[10] | | X | X[10] | | X | X | X |
| **MMSE** | **X** | **X** | | **X** | | | | | | | **X[11]** | | **X[11]** | | **X** |
| ~~Urine~~ Pregnancy Test[13][15] | X | X[10] | | | X[10] | | | X[10] | | | X[10] | | | | X |

[5] May be performed at any time on the day prior to study treatment administration, ~~or~~ predose on the day of study treatment administration, or over 2 days at the **Follow-up Visits (Weeks 240 and 244) and** Final or Early Termination Visit.

~~[10] To be collected/performed predose.~~

**[11] To be performed at Week 12, 24, 36, and 48 Visits (i.e., every 12 weeks); Week 72, 96, 120, 144, 168, 192, and 216 Visits (i.e., every 24 weeks); and Week 228 Visit.**

~~[12]~~**[14]** The components of the limited neurological examination are ~~cranial nerves,~~ coordination/cerebellar function, reflexes, **and** motor **system**~~, and MMSE~~.

~~[13]~~**[15]** To be performed only in women of childbearing potential; results must be negative to continue participation in study. On dosing days, samples must be analyzed before study treatment administration. **To be performed via urine or serum testing.**

**Rationale:** [redacted] No findings of concern have been noted on the MMSE during Study 233AS101 or 233AS102, so the frequency of the MMSE assessment was reduced to every 3 months during the treatment period. Likewise, no findings of concern have been seen in the cranial nerve examination, so this was removed to align with Part C of Study 233AS101 and to reduce subject burden. Changes to pregnancy testing were made to allow flexibility at the site and to align with Part C of Study 233AS101.

These changes also affect Section 14.1, Clinical Safety Assessments, Section 14.2, Laboratory Safety Assessments, Section 16.5.2.5, Limited Neurological Examination, and Section 19.1.4, Central Laboratories for Laboratory Assessments.

Section 8.2, Exclusion Criteria

**Change:** Exclusion criterion 1 excluding subjects with current or prior hepatitis B infection and exclusion criterion 8 excluding the presence of an implanted intravenous port/catheter were removed. Exclusion criterion 15 was updated. All subsequent exclusion criteria were renumbered accordingly.

**Now reads:**

~~1. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [anti-HBc]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive IgM anti-HBc, and positive anti-HBc) or vaccination (defined as positive anti-HBs) are eligible to participate in the study.~~

~~8. Presence of an implanted intravenous port/catheter.~~

~~15~~13. Anticipated need, in the opinion of the Investigator, for administration of any antiplatelet or anticoagulant medication ~~(e.g., clopidogrel) for 7 days~~ **that cannot be safely continued or held for** ~~before or 48 hours after~~ an LP procedure, **if necessary, according to local or institutional guidelines and/or Investigator determination**.

**Rationale:** Subjects in Study 233AS102 were previously enrolled in Study 233AS101 and were therefore screened for hepatitis B based on the exclusion criteria for Study 233AS101. There is no requirement in Study 233AS101 that a subject must discontinue study treatment if they acquire hepatitis B during the course of the study. The requirement for repeat screening is therefore not necessary for subjects to roll into Study 233AS102.

Exclusion criterion 8 excluding the presence of an implanted intravenous port/catheter was removed for subjects who entered this study from Parts A or B of Study 233AS101 because its use is not precluded in Study 233AS101.

Because study treatment administration will occur via lumbar puncture, care must be exercised in the use of antiplatelet or anticoagulant medication. Exclusion criterion 13 (previously exclusion criterion 15) has been updated to allow for the Investigator's clinical judgement and local standard of care to be used, accounting for the many different indications, medications, and individual subject situations that may be relevant.

This change also affects Section 4, Schedule of Activities, Table 1 and Section 11.3.1.2, Disallowed Concomitant Therapy.

Section 9.1, Screening and Enrollment

**Change:** Language was added to allow rescreening of subjects.

**Now reads:**

~~Eligible subjects who are not able to complete the Day 1 Visit within 28 days of starting their screening assessments may be rescreened.~~ **Subjects who fail screening can be rescreened once at the discretion of the Investigator. All rescreening must be completed within 56 calendar days after the start of the screening period (Study 233AS101 Day 169 [Week 24 Visit]).**

**Rationale:** This was done to prevent the exclusion of subjects due to a transitory issue with a screening result.

Section 13.1.3, Subject Diaries

**Change:** Section 13.1.3, Subject Dairies was added.

**Now reads:**

At Screening, subjects will be given diaries to record the date and time of ventilation use. This diary will be reviewed with study site staff at each visit. Refer to the Study Reference Guide for details.

**Rationale:** This was added to align with Section 4, Schedule of Activities for Study 233AS102, Table 1 and Biogen template.

This change affects all subsequent header numbering within Section 13.1, Clinical Function Assessments.

Section 13.4, Genomic and Pharmacogenomic Assessments

**Change:** Section 13.4, Genomic and Pharmacogenomic Assessments, was added.

**Now reads:**

**For subjects who did not have the presence or absence of a SOD1 mutation confirmed centrally in Study 233AS101, a one-time blood sample will be collected. For subjects who did not have a blood sample collected for testing of other genes related to ALS and/or the response to BIIB067 in Study 233AS101, an additional blood sample will be collected. The main ICF will govern use of these samples in genetic analyses to understand ALS and the response to BIIB067 in the context of this clinical program.**

**In addition, where not prohibited by regulatory authorities or ethics committees, an optional genetic consent will be offered to these subjects to allow samples to be stored for future unspecified genetic research related to other diseases and traits of interest to Biogen.**

**Approximately 10% of ALS is known to be caused by genetic mutations; to date, at least 20 genes have been identified as causative of or highly associated with ALS, including SOD1. The DNA sample will be analyzed for genetic variation in the SOD1 gene to determine the spectrum of likely pathogenic mutations in the gene and to assess if SOD1 polymorphisms affect response to treatment. In addition, samples collected during the study may be analyzed for genetic variation in other genes of known and probable relevance for the pathogenesis of ALS and neurodegeneration, including but not limited to TAR DNA binding protein (TARDBP), FUS (fused in sarcoma), C9ORF72, optineurin (OPTN), valosin-containing protein (VCP), ubiquilin 2 (UBQLN2), profilin 1 (PFN1), and ataxin (ATXN2).**

**In the event of an unusual response or observation of unexplained AEs, DNA samples may be used to determine if there are any pharmacogenomics associations with drug response.**

**In the future, as our understanding of ALS and BIIB067 increases, additional genomic analyses may be warranted to refine the knowledge of the molecular basis of the disease and the drug response as well as to advance the development of novel therapeutics. The sample will only be used in genetic analyses to understand ALS, neurodegeneration, and response to BIIB067.**

**The DNA samples will be coded and may be stored for up to 15 years. No genotyping or genomic data will be provided back to the subject. Subjects may withdraw consent and request to have their samples destroyed at any time and no further genetic data will be generated; any data already generated will not be destroyed.**

**Rationale:** Genetic polymorphisms affecting genes encoding drug targets or relevant biological pathways, as well as proteins that affect drug absorption, distribution, metabolism, and elimination, may affect the safety and efficacy of the study treatment. To assess this, samples will be collected for testing genes related to amyotrophic lateral sclerosis and/or the response to BIIB067. Samples will only be collected from subjects who had not previously provided them in Study 233AS101.

This change also affects Section 4, Schedule of Activities for Study 233AS102, Table 1.

## SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- Sponsor Signature Page was updated to reflect the signatory's current title.
- The abbreviation [redacted] was updated throughout.
- Editorial change describing the "effects on disease progression of BIIB067" was updated throughout to "efficacy of BIIB067."
- Language describing the study as an "open-label, long-term extension study" was clarified throughout.
- Telephone call was updated to telephone contact throughout the protocol to allow contact via text messaging.
- Clarification was added throughout the protocol that home visit/assessments may be allowed at the discretion of the Investigator.
- Typographical errors and formatting were corrected.
- Section 2, List of Abbreviations, was updated.
- Section 4, Schedule of Activities for Study 233AS102, Table 1, the following minor changes were made to reduce redundancies and/or for clarity:
  - "Clinical Laboratory Samples to Verify Eligibility Criteria" was changed to now read "Confirmation of Eligibility Criteria" for clarity, since laboratory samples were already being collected during the Screening Visit.
  - Footnote 3 (previously footnote 2) was reworded for clarity. This change also affects Section 8.1 Inclusion Criteria, criterion 6.
  - Footnote 4 was updated to reference the Study Reference Guide for details. This change also affects Section 13.1.3, Subject Diary.
  - Footnote 5 was updated to include the Follow-up Visits such that assessments at the Follow-up Visits may be collected over 2 days similar to the Final or Early Termination Visit.

  - Footnote 10 were removed due to redundancy.

  - Footnote 16 (previously footnote 14) was updated with additional details regarding CSF collection during LP, evaluation for contamination, and safety testing at local labs.

  - The numbering of the footnotes and the abbreviations were adjusted accordingly.

- Section 5.2, Current Therapies for Amyotrophic Lateral Sclerosis, information was generalized to include only the generic names riluzole and edaravone, and details on approval status in different countries were removed.

- Section 5.3.2, Clinical Experience, was updated to include interim analysis results for Part A (single ascending dose) and Part B (multiple ascending dose) of this study. This change also affects Section 5.5, Rationale for Dosing Regimen.

- Section 5.4, Study Rationale, editorial changes were made for clarity.

- Section 7.1, Study Overview, was updated with the total number of countries and number of planned sites globally and to clarify that the last Maintenance Dose Visit for subjects will occur at Week 236 OR when the last subject enrolled has had his or her Week 92 Maintenance Dose Visit, whichever occurs first.

- Section 7.2.2, Dosing, was updated to clarify that Day 1 of this study should occur no earlier than 28 days after the subject's last dose (i.e., Day 169 [Week 24 Visit]) in Study 233AS101 to prevent subjects from being dosed too soon.

- Section 8.1, Inclusion Criteria, criterion 7 was updated to clarify that this applied only to female subjects of childbearing potential.

- Section 13.1, Clinical Function, Pharmacokinetic, and Pharmacodynamic Assessments, was updated to clarify that all study visits are expected to occur at the site, unless the subject is unable to travel to the site; then, a home visit may be possible at the discretion of the Investigator.

- Section 13.1.1, ALS Functional Rating Scale-Revised, was updated to include for each site that the same qualified and trained study site staff member will consistently perform the ALSFRS-R for a subject and that a qualified and trained backup ALSFRS-R rater will be identified in case the primary rater is unavailable.

- Section 13.1.2, Slow Vital Capacity, was updated to note that at least 3 acceptable tests with the 2 highest acceptable (largest and next largest) efforts within 150 mL of vital capacity are required for slow vital capacity (SVC) testing. This change also affects Section 4, Schedule of Activities for Study 233AS102, Table 1 (the addition of footnote 7). Additionally, a statement was added to clarify that the SVC would be performed according to the study Pulmonary Procedure Manual.

- [redacted]

- Section 13.3.1, Future Scientific Research Assessments, was updated to clarify that that samples will be collected for future research purposes where not prohibited by regulatory authorities or ethics committees and to clarify what samples may be collected.

- Section 15.2.2, Relationship of Events to Study Treatment, section heading was updated to more accurately reflect its content (i.e. include LP.

- Section 15.4.1, Pregnancy, the requirement that male subjects do not impregnate their partner during the study and for 5 months after their last dose of study treatment was removed to make language consistent with the language in Section 15.5, Contraception Requirements, where it had been removed in Protocol Version 4 based on findings from a reproductive toxicology study.

- Section 15.5, Contraception Requirements, was updated to clarify that at least 1 contraception method stated was required.

- Section 16.1.1, Analysis Population, was updated to remove the requirement that subjects must have at least 1 available postdosing evaluation of the respective clinical function endpoint to be included in the analysis population.

- [redacted].

- Section 19.1.3, Electronic Data Capture, was updated to allow the use of eDiaries in the future to record ventilation use.

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# AMENDMENT SUMMARY

Biogen Protocol 233AS102

An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation

Version 4

Date: 11 January 2019

EUDRA CT: 2016-003225-41

Version 4 of the protocol has been prepared for this amendment, which supersedes Version 3.

# PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 233AS102 is to further extend the study duration that will allow any and all subjects to receive treatment until either the subject's Final Visit at Week 248 or until the last subject randomized has had his or her Week 92 Visit, whichever occurs first.

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

Section 7.2, Overall Study Duration and Follow-Up (previously Section 7.3 in Protocol Version 3)

**Now reads:**

~~7.3.~~**7.2.** Overall Study Duration and Follow-Up

The overall duration of study participation for a single subject will be approximately ~~757 days (i.e., 27 months),~~**up to 252 weeks,** which includes an approximately ~~28 day~~**4-week** screening period, **up to** a ~~645 day (i.e., 23 month)~~**236-week** treatment period, and ~~an 84 day (i.e., 3 month)~~ **a 12-week** follow-up period.

~~7.3.1.~~**7.2.1**. Screening

**7.2.1.1. Subjects Who Have Completed Parts A and B of Study 233AS101**

Subjects who ~~complete~~ **have completed** Part B (MAD) of Study 233AS101 ~~(up to 48~~ **and** subjects~~)~~ ~~and subjects with SOD1 ALS~~ who ~~complete~~ **have completed** Part A (single ascending dose~~)~~ **[SAD]**~~,~~) of that study will be eligible for screening. Subject eligibility for the study will be determined from ~~Day -28~~ **Week -4** through Day -1.

The Screening Visit assessments may be performed over approximately 2 days, which do not need to be consecutive, to minimize subject burden. All assessments must be completed **on or** before the ~~baseline/loading dose visit~~ **Baseline/Loading Dose Visit** on Day 1.

**7.2.1.2. Subjects Who Have Completed Part C of Study 233AS101**

**Subjects who have completed the last dosing visit in Part C of Study 233AS101 will be able to screen to determine eligibility to participate in Study 233AS102. A subject's last dosing visit in Part C of Study 233AS101 will be the start of the Screening Visit (Week -4 to Day -1) for this open-label extension Study 233AS102. Results from assessments completed by subjects at the last dosing visit of Study 233AS101 can be used for the purpose of screening and do not need to be repeated as long as they are conducted within 4 weeks of the Baseline/Loading Dose Visit on Day 1.**

~~7.3.2.~~**7.2.2.** Dosing

Eligible subjects will report to the study site on Day 1 to complete baseline assessments and reaffirm eligibility. ~~Subjects will receive 3 loading doses of BIIB067 approximately 2 weeks apart (Day 1, Day 15, and Day 29), during the 29-day loading dose period.~~

~~During the maintenance portion of the study, subjects will receive 22 doses of BIIB067 approximately every 4 weeks, during visits on Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, and 645 (i.e., Month 3 to Month 24).~~

**Assessments collected at the Follow-up Visit (4 weeks after last dose) of Part C of Study 233AS101 will be used as the Day 1 predose assessments for Study 233AS102 if they are collected within 48 hours of the first dose in Study 233AS102.**

**On dosing days, subjects will remain** ~~under observation for approximately 6 hours after the lumbar puncture (LP)~~ **at the study site for at least 1 hour postdose for safety monitoring and can be discharged at the discretion of the Investigator and in compliance with the institutional requirements, once the subjects have adequately recovered from the dosing procedure. Subjects** will receive a safety follow-up telephone call approximately 24 hours after the procedure.

7.2.2.1. **Loading Dose Period**

**The Loading Dose Period of the study will occur from Day 1 to Day 29.**

- **Subjects who have completed Parts A or B of Study 233AS101:**
  - **Subjects will receive 3 loading doses of BIIB067 approximately 2 weeks apart (Day 1, Day 15, and Day 29**~~), during the 29 day loading dose period. )~~.
- **Subjects who have completed Part C of Study 233AS101:**
  - **Subjects randomized to receive placebo during Study 233AS101 will receive 3 loading doses of BIIB067, approximately 2 weeks apart (Day 1, Day 15, and Day 29). The Investigators, study staff (except for an unblinded designated pharmacist/technician), and study subjects will be blinded to the study treatment during the Loading Dose Period.**
  - **Subjects randomized to receive BIIB067 during Study 233AS101 will receive 2 loading doses of BIIB067, on Days 1 and 29, and 1 dose of placebo, on Day 15. The Investigators, study staff (except for an unblinded designated pharmacist/technician), and study subjects will be blinded to the study treatment during the Loading Dose Period.**

**7.2.2.2. Maintenance Dose Period**

During the maintenance portion of the study, subjects will receive ~~22~~ **up to 58 doses** of BIIB067**,** approximately every 4 weeks, during visits ~~on Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, and 645 (i.e., Month 3 to Month 24).~~**at Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 236, OR when the last subject enrolled has had their Week 92 Maintenance Dose Visit, whichever occurs first**.

~~On dosing days, subjects will remain under observation for approximately 6 hours after the lumbar puncture (LP) procedure and will receive a safety follow-up telephone call approximately 24 hours after the procedure.~~

~~7.3.3.~~**7.2.3.** Follow-Up

Subjects will return for Follow-Up Visits ~~on Day 673, Day 701~~**at Weeks 240 and 244**, and ~~Day 729 (i.e., Month 25, Month 26, and Month 27 [~~**for the Final Visit at Week 248 OR for early withdrawals at 4, 8, and 12 weeks (**~~Final/~~Early Termination Visit~~]).~~**) after their last dose**. CSF sampling will be performed ~~on~~ **at** either ~~Day 673 (i.e., Month 25)~~ **Week 240** or ~~Day 701 (i.e., Month 26), and on Day 729 (i.e., Month 27).~~**Week 244 or for early withdrawals 4 or 8 weeks after their last dose**. On the day of CSF sampling during the follow-up ~~periods~~ **period**, subjects will remain under observation in the clinic for approximately 1 hour after the LP procedure and will receive a safety follow-up telephone call approximately 24 hours after the procedure.

**Rationale:** The primary reason for extending the study is to allow the collection of additional data beyond 2 years to evaluate the long-term efficacy and safety of BIIB067.

This change also affects Section 3, Synopsis; Section 4, Study Schematic and Schedule of Activities for Study 233AS102; Section 7.4, Study Stopping Rules; Section 7.5, End of Study; Section 11, Study Treatment Use; Section 15.3, Monitoring and Recording Events; and Section 16.3, Pharmacodynamics.

# SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Title Page

**Change:** The phase of development was updated to accurately reflect the need of the long-term extension study.

**Now reads:**

PHASE OF DEVELOPMENT: ~~1~~**3**

**Rationale:** This change was made to align the Study 233AS102 development with that of Study 233AS101.

Section 3, Synopsis

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

Section 4, Study Schematic and Schedule of Activities for Study 233AS102

**Change:** Figure 1 was removed from the document.

Table 1 was updated to make the following changes to

- Reflect when in relation (pre-, during, or post- lumbar puncture [LP]) to the LP assessments were to be collected
- Order the assessments to reflect the order in which they are to be collected during a visit
- Change days to weeks
- No longer require collection of EIM
- [redacted]
- Remove the ECG collection at Day 15 Visit

[redacted]

Footnotes were also updated to appropriately reflect and clarify these changes.

**Now reads:**

## Table 1: Schedule of Activities

| Assessments | Screening Visit[1] | Baseline/1st Loading Dose Visit | | | 2nd Loading Dose Visit | | | 3rd Loading Dose Visit | | | Maintenance Dose Visit ~~Visits~~ | | | Follow-Up Visit ~~Visits~~ | Final~~/~~ or Early Termination Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ~~Day~~ 28Week -4 to Day -1 | Day 1 | | | Day 15 (±3 days) (Week 2) | | | Day 29 (±3 days) (Week 4) | | | ~~Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, & 645 (i.e., Months 3-24)~~Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 236 (±3 days) | | | ~~Days 673 & 701 (i.e., Months 25 & 26)~~ Weeks 240 and 244 (±7 days) (4 and 8 weeks after last dose) | ~~Day 729 (i.e., Month 27)~~Week 248 (±7 days) 12 weeks after last dose [Early Termination Visit] |
| | | Pre dose | LP | Post dose | Pre dose | LP | Post dose | Pre dose | LP | Post dose | Pre dose | LP | Post dose | | |
| Informed Consent Form (main) and Genetic/Future Scientific Research Consent (optional) | X | | | | | | | | | | | | | | |
| Medical History | X | X | | | | | | | | | | | | | |
| Clinical Laboratory Samples to Verify Eligibility[2,3] | X | | | | | | | | | | | | | | |
| **Ventilation Use[4]** | | **X** | | | **X** | | | **X** | | | **X** | | | **X** | **X** |
| ALSFRS-R | | X~~95~~ | | | X~~995~~ | | | X~~995~~ | | | X~~995,6~~ | | | X | X~~995~~ |
| SVC | | X~~995~~ | | | X~~995~~ | | | X~~995~~ | | | X~~995,~~ | | | X | X~~995~~ |
| HHD | | X~~995~~ | | | X~~995~~ | | | X~~995~~ | | | X~~995,6~~ | | | X | X~~995~~ |
| [redacted] | | | | | | | | | | | | | | | |

| **Assessments** | **Screening Visit**[1] | **Baseline/1st Loading Dose Visit** | | | **2nd Loading Dose Visit** | | | **3rd Loading Dose Visit** | | | **Maintenance Dose Visit ~~Visits~~** | | | **Follow-Up Visit ~~Visits~~** | **Final~~/~~ or Early Termination Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **~~Day 28~~Week -4 to Day -1** | **Day 1** | | | **Day 15 (±3 days) (Week 2)** | | | **Day 29 (±3 days) (Week 4)** | | | **~~Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, & 645 (i.e., Months 3-24)~~Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 236 (±3 days)** | | | **~~Days 673 & 701 (i.e., Months 25 & 26)~~ Weeks 240 and 244 (±7 days) (4 and 8 weeks after last dose)** | **~~Day 729 (i.e., Month 27)~~Week 248 (±7 days) 12 weeks after last dose [Early Termination Visit]** |
| | | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | | |
| [redacted] | | | | | | | | | | | | | | | |
| C-SSRS[9] | | X | | | | | | X | | | X[6] | | | X | X |
| Weight | X | X~~[5]~~[10] | | | | | | | | | | | | | X |
| Vital Signs (temperature, blood pressure, pulse rate, respiratory rate) | X | X~~[5]~~[11] | | X | X | | X | X~~[5]~~[12] | | X | X~~[5]~~[13] | | X | X | X |
| 12-lead EC[14] | X | X~~[5]~~[15] | | | | | | X~~[5]~~[16] | | | X~~[5]~~[17] | | | X | X |
| Physical Examination | X | X~~[5]~~[18] | | | X~~[5]~~[19] | | | X~~[5]~~[20] | | | X~~[5]~~[21] | | | X | X |
| Limited Neurological Examination (including MMSE)~~[4]~~[22] | X | X~~[5]~~[23] | | X | X~~[5]~~[24] | | X | X~~[5]~~[25] | | X | X~~[5]~~[26] | | X | X | X |

| **Assessments** | **Screening Visit**[1] | **Baseline/1st Loading Dose Visit** | | | **2nd Loading Dose Visit** | | | **3rd Loading Dose Visit** | | | **Maintenance Dose Visit ~~Visits~~** | | | **Follow-Up Visit ~~Visits~~** | **Final~~/~~ or Early Termination Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **~~Day 28~~Week -4 to Day -1** | **Day 1** | | | **Day 15 (±3 days) (Week 2)** | | | **Day 29 (±3 days) (Week 4)** | | | **~~Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, & 645 (i.e., Months 3-24)~~Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 236 (±3 days)** | | | **~~Days 673 & 701 (i.e., Months 25 & 26)~~ Weeks 240 and 244 (±7 days) (4 and 8 weeks after last dose)** | **~~Day 729 (i.e., Month 27)~~Week 248 (±7 days) 12 weeks after last dose [Early Termination Visit]** |
| | | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | | |
| Urine Pregnancy Test[27] | X | X~~[28]~~ | | | X~~[29]~~ | | | X~~[30]~~ | | | X~~[31]~~ | | | | X |
| CSF Samples[32] | | X~~[5,13]~~ [33,34] | | | X~~[5,13]~~ [35,36] | | | X~~[5,13]~~ [37,38] | | | X~~[5,13]~~ [39,40] | | | ~~X[5,13]~~ | ~~X[5,13]~~ |
| Clinical Laboratory Samples for Hematology, Coagulation, Chemistry, and Urinalysis | X | X | | | X | | | X | | | X | | | X | X |
| [redacted] | | | | | | | | | | | | | | | |
| Blood Samples for Plasma anti-BIIB067 Ab | | X~~[45]~~ | | | X~~[46]~~ | | | X~~[47]~~ | | | X~~[5]~~ [48,49] | | | | X |
| Blood Samples for PK | | X~~[50]~~ | | | X~~[51]~~ | | | X~~[52]~~ | | | X~~[5]~~ [53,54] | | | | X |
| Blood Samples for PD and Biomarkers | | X~~[55]~~ | | | X~~[56]~~ | | | X~~[57]~~ | | | X~~[58]~~ | | | | X |
| [redacted] | | | | | | | | | | | | | | | |
| Study Treatment Administration | | | X | | | X | | | X | | | X | | | |
| ~~Adverse Event~~ **AE**/Concomitant Therapy and Procedures Recording | | ----------X (ongoing)---------- | | | | | | | | | | | | | |

| **Assessments** | **Screening Visit**[1] | **Baseline/1st Loading Dose Visit** | | | **2nd Loading Dose Visit** | | | **3rd Loading Dose Visit** | | | **Maintenance Dose Visit ~~Visits~~** | | | **Follow-Up Visit ~~Visits~~** | **Final~~/~~ or Early Termination Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **~~Day 28~~Week -4 to Day -1** | **Day 1** | | | **Day 15 (±3 days) (Week 2)** | | | **Day 29 (±3 days) (Week 4)** | | | **~~Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, & 645 (i.e., Months 3-24)~~Weeks 8, 12, 16, and every 4 weeks thereafter up to Week 236 (±3 days)** | | | **~~Days 673 & 701 (i.e., Months 25 & 26)~~ Weeks 240 and 244 (±7 days) (4 and 8 weeks after last dose)** | **~~Day 729 (i.e., Month 27)~~Week 248 (±7 days) 12 weeks after last dose [Early Termination Visit]** |
| | | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | **Pre dose** | **LP** | **Post dose** | | |
| SAE Recording | ----------X (ongoing)---------- | | | | | | | | | | | | | | |

Ab = antibody; **AE = adverse event;** [redacted]; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram, ~~EIM = electrical impedance myography;~~ [redacted] HHD = handheld dynamometry; **LP = lumbar puncture;** MMSE = Mini-~~mental~~**Mental** State Examination; [redacted] PD = pharmacodynamics; PK = pharmacokinetics; RNA = ribonucleic acid; **SAE = serious adverse event;** [redacted] SVC = slow vital capacity; [redacted].

1 Screening assessments can be performed over ~2 days (need not be consecutive) to minimize subject burden.

2 Including blood samples for human immunodeficiency virus, hepatitis C virus, and hepatitis B virus tests, and platelet and coagulation tests. Platelet and coagulation tests may be repeated at the local laboratory once if, in the opinion of the Investigator, the values of the initial tests are only slightly out of range.

3 Results of coagulation tests and platelet count must be reviewed before a lumbar puncture can be performed. Should the results obtained at a prior screening, dosing, or Follow-Up Visit suggest, in the opinion of the Investigator, that a tap may be safely performed then no additional laboratory values would require review before performing the lumbar puncture. However, should repeat coagulation and platelet tests be clinically indicated in the opinion of the Investigator, then these tests may be done locally to facilitate timely review.

~~4 The components of the limited neurological examination are cranial nerves, coordination/cerebellar function, reflexes, motor, and MMSE.~~

**[5][4] Subjects will use a diary to record ventilation use. This diary will be reviewed with study site staff at each visit.**

**[5] May be performed at any time on the day prior to study treatment administration or predose on the day of study treatment administration, or over 2 days at the Final or ~~/~~Early Termination Visit.**

**[6] To be performed at Week 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, and 236 (i.e., every 4 weeks) Visits only.**

[redacted]

[redacted]

[9] **"Since Last Visit" version of C-SSRS will be used after the Baseline/First Loading Dosing Visit.**

[10] **To be collected/performed predose.**

[6][11] Triplicate 12-lead (paper) ECGs will be obtained after subjects have rested in a supine position for at least 10 minutes. The first ECG will be interpreted, and the last 2 ECGs will be checked for consistency and quality.

~~[7] "Since Last Visit" version of C-SSRS will be used after the Baseline/1st Dosing Visit.~~

[8][12] **The components of the limited neurological examination are cranial nerves, coordination/cerebellar function, reflexes, motor, and MMSE.**

[13] To be performed only in women of childbearing potential; results must be negative to continue participation in study. On dosing days, samples must be analyzed before study treatment administration.

~~[9] May be performed at any time on the day prior to study treatment administration or predose on the day of study treatment administration, or over 2 days at the Final/Early Termination Visit.~~

~~[10] To be performed at Days 141, 309, 477, and 645 (i.e., Months 6, 12, 18 and 24) Visits only.~~

~~[11] To be performed at Days 85, 141, 197, 253, 309, 365, 421, 477, 533, 589, and 645 (i.e., Months 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24) Visits only.~~

[12][14] Lumbar puncture will be performed to collect CSF samples for PK, PD, safety, and biomarker analysis.

~~[13] Subjects will remain under observation in the clinic for ~ 6 hours after the lumbar puncture procedure and will receive a safety follow-up telephone call ~ 24 hours after the procedure.~~

[14][15] Subjects will remain under observation in the clinic for ~1 hour after the lumbar puncture procedure ~~and~~ **for safety monitoring and can be discharged at the discretion of the Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the procedure. Subjects** will receive a safety follow-up telephone call ~24 hours after the procedure. ~~The procedure at the Follow-up Visits may be performed at the Day 673 (i.e., Month 25) or Day 701 (i.e., Month 26) Visit~~.

[15][16] **Blood samples will be collected on every alternate visit at Week 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148, 156, 164, 172, 180, 188, 196, 204, 212, 220, 228, and 236 (i.e., every 8 weeks) Visits only. Blood samples for anti-BIIB067 Ab and PK assessments will be collected at the same time.**

[17] Subjects who agree to provide samples will need to sign separate consent form(s). RNA sample collection for possible future research will be optional in all regions where not prohibited by regulatory authorities or ethics committees.

**Rationale:** These changes were made to align the assessments of this study with those in Part C of Study 233AS101, to provide clarity (days to weeks and relation to LP), and to minimize the burden to the subject while preserving data and study integrity (changes to assessment frequency).

This change also affects [redacted]; Section 7.3, Overall Study Duration and Follow-up; Section 13.1, Clinical Function Assessments; and Section 16.1.2, Methods of Analysis.

Section 5.4, Study Rationale

**Change:** Study rationale text was updated with the evaluation of PD, PK, and effect of disease progression of BIIB067.

**Now reads:**

This study will evaluate the long-term safety, tolerability, **PD, PK**, and ~~**PK**~~ **effect of disease progression** of BIIB067 ~~in~~ **administered to** subjects with SOD1-ALS who have completed ~~Part~~ **Parts** A ~~and/or~~ B**, or C** of the FIH study (233AS101) of BIIB067.

~~The study will also characterize the effects of BIIB067 on disease progression by examining changes over time in clinical, electrophysiologic,~~ [redacted] ~~assessments of individual subjects~~

~~The extension study will allow collection of PK and pharmacodynamics (PD) data during dose interruption and resumption, thereby providing valuable information on the dynamic behavior of the system. This information will augment the PK and PD data collected in the FIH Study 233AS101 for the purpose of creating models of the exposure response relationship. These models will be used to simulate and assess PD profiles under various dosing regimens and will inform the dose levels of BIIB067 and frequencies to be tested in future studies.~~

**Rationale:** This change was made to align the rationale with Study 233AS101 and for clarity.

This change also affects Section 6, Study Objectives and Endpoints.

Section 5.5, Rationale for Dosing Regimen

**Change:** All subjects in Study 233AS102 will now be dosed at 100 mg BIIB067.

**Now reads:**

~~Doses in this extension study~~**BIIB067** will be ~~the same as in Part B of Study 233AS101~~ **administered via IT bolus at 100 mg**.

The BIIB067 dosing regimens for **Parts A and B of** Study 233AS101 were selected based on target tissue concentrations from SOD1 transgenic mouse models, and nonclinical toxicology and PK observations in repeated dose, IT administration in 13 week and 9 month nonhuman primate (NHP) studies.

The lowest dose selected for Study 233AS101 (10 mg **in Part A**) was predicted to achieve greater than 0.9 µg/g tissue concentration in the spinal cord. The initial highest proposed dose (60 mg, multiple dose **in Part B**) was predicted to achieve greater than 4.7 µg/g steady state tissue concentration in the spinal cord, and approximately 1.5 µg/g steady state tissue concentration in the cortex, which is expected to yield approximately 15% to 20% SOD1 mRNA reduction in that tissue.

~~Therefore, all~~ **For Part C (Pivotal) of Study 233AS101, the dose of 100 mg of** BIIB067 **was determined based on the interim analyses of data from subjects in Part B (MAD) Cohorts 5 to 8 treated for 85 days. Safety analyses of these data suggested that all** doses ~~planned for Studies 233AS101 and 233AS102 are predicted to be pharmacologically active, while maintaining sufficient~~ **through 100 mg had been well tolerated, with a** safety ~~margins calculated from the 9 month IT NHP toxicology study.~~ **profile supportive of continued development of BIIB067 in subjects with ALS**.

**Rationale:** The 100 mg dose of BIIB067 was determined based on the interim analyses of data from Study 233AS101.

Section 6, Study Objectives and Endpoints

**Change:** Clarified that study objectives were being assessed in subjects with ALS and confirmed SOD1 mutation. Study secondary and exploratory objectives/endpoints were rearranged and segregated using subheadings. The secondary objective was updated to include disease progression. As a result, the ALSFRS-R scores, SVC, and HHD scores [redacted] were changed to secondary endpoints, and the VAFS and overall survival were added as secondary endpoints. [redacted]

**Now reads:**

6.1. Primary Objective and Endpoints

The primary objective of the study is to evaluate the long-term safety and tolerability of BIIB067 in subjects with **ALS and confirmed** SOD1 ~~ALS mutation~~.

The associated primary endpoints are the incidence of AEs and serious adverse events (SAEs).

6.2. Secondary Objectives and Endpoints

The secondary ~~objective is~~ **objectives are** to evaluate the PK **and PD** profile**s and effects on disease progression** of BIIB067 ~~in~~ **administered to** subjects with **ALS and confirmed** SOD1 ~~ALS~~ mutation.

### 6.2.1. Pharmacokinetic Endpoints

The ~~associated secondary~~ **PK** endpoints are ~~PK measures, including~~ plasma and CSF levels of BIIB067 ~~and CSF levels of the SOD1 protein~~.

[redacted]

### 6.2.2. Pharmacodynamic Endpoints

The [redacted] ~~of this study and the associated~~ PD endpoints are as follows:

~~To evaluate the PD profile of BIIB067 in subjects with SOD1 ALS by examining~~ changes from baseline in ~~potential biomarker measures, which may include, but not be limited to~~ total CSF SOD1 [redacted]

6.2.3. ~~To evaluate the effects of BIIB067 on disease progression in each individual subject by examining~~ **Disease Progression Endpoints**

**Disease progression endpoints are** changes over time in the following:

- ALSFRS-R scores
- Slow vital capacity (SVC)
  - [redacted]
  - [redacted]
- Handheld dynamometry (HHD) scores
- **Ventilation assistance-free survival (VAFS), which is defined as the time to the earliest occurrence of one of the following events:**
  - **Death.**
  - **First use of noninvasive ventilation (NIV) for ≥22 hours per day for ≥10 consecutive days.**
  - **First use of permanent assisted ventilation (PAV) for ≥22 hours per day for ≥7 consecutive days.**
- **Overall survival**

[redacted]

[redacted]

**Rationale:** Subjects must have both amyotrophic lateral sclerosis (ALS) and confirmed superoxide dismutase 1 (SOD1) mutation to be enrolled in this study from Study 233AS101. All the secondary and exploratory objectives/endpoints were aligned with those of Study 233AS101.

[redacted]

Section 7.1, Study Overview and Section 7.2, Study Specifics

**Change:** Deleted uncontrolled from the study design, and allowed participation of subjects who have completed Part C of Study 233AS101; added text for all subjects who have completed Parts A, B, or C of Study 233AS101 to receive 100 mg BIIB067, regardless of their treatment dose in Study 233AS101 or prior dosing in Study 233AS102; and specified that subjects who have completed Part C of Study 233AS101 do not need to undergo a washout period but are required to undergo a loading dose period. Blinding procedures were updated for subjects enrolling from Part C of Study 233AS101. Study-specific sections for subjects who have completed Parts A or B of Study 233AS101 and were participating in the current study were also deleted.

**Now reads:**

7.1. Study Overview

This is a multicenter, open-label, ~~uncontrolled,~~ extension study to assess the long-term safety, tolerability**, PD**, PK, and effect on disease progression of BIIB067 administered by IT injection to previously treated subjects with SOD1-ALS who have completed ~~Part~~ **Parts** A ~~and~~/**, B,** or ~~Part B~~ **C** of Study 233AS101. The study will be conducted at approximately ~~16~~ **18** sites in the United States, Canada, **Japan,** and Western Europe.

~~In Study 233AS101, the Investigators, study staff (except for a designated pharmacist/technician), and study subjects are blinded to the randomized study treatment assignments. To preserve the blinding used in Study 233AS101 until database lock, subjects in Study 233AS102 will have a washout period~~ **Subjects who have completed Parts A or B of Study 233AS101 will have a washout period** of at least 4 times the t½ (~16 weeks) from the time of their last dose of study treatment in Study 233AS101 to their first dose in

Study 233AS102. ~~Subjects~~ **These subjects** will receive 3 loading doses of **100 mg** BIIB067, approximately 2 weeks apart, during the first 4 weeks ~~and 22 maintenance doses, approximately every 4 weeks, by IT injection~~.

~~Initial dose level assignment for each subject who completes~~ **Subjects who have completed** Part ~~B~~ C of Study 233AS101 will ~~correspond to their cohort assignment~~ **not have a washout period. To preserve the blinding used** in Study 233AS101~~, regardless of whether~~ **they until database lock, subjects who enroll in Study 233AS102 after completing Part C of Study 233AS101 will have a blinded Loading Dose Period. Subjects who** received ~~BIIB067 or~~ placebo~~. All subjects randomized to Cohort 5 (BIIB067 20 mg or placebo)~~ **while** in Study 233AS101 will receive **3 doses of 100 mg BIIB067, approximately once every 2 weeks (Days 1, 15, and 29), while subjects who received BIIB067 in Study 233AS101 will receive 2 doses of 100 mg** BIIB067 ~~20 mg;~~**, on Days 1 and 29, and placebo on Day 15**.

**After the Loading Dose Period, all** subjects ~~who were randomized~~ **will receive up** to ~~Cohort 6 (~~**58 maintenance doses of 100 mg** BIIB067 ~~40 mg or placebo) will receive,~~ **approximately every 4 weeks, by IT injection. Subjects who were not receiving 100 mg** BIIB067 ~~40 mg, those randomized to Cohort 7 (BIIB067 60 mg or placebo) will receive BIIB067 60 mg, and those randomized to Cohort 8 (BIIB067 100 mg or placebo) will receive BIIB067 100 mg. If the highest dose (100 mg) is dropped based on results from the multiple ascending dose (MAD) portion (Part B) of Study 233AS101, subjects in Cohort 8~~, will be ~~placed in the 60 mg cohort in this extension study.~~

~~Subjects who complete only Part A of Study 233AS101 will be assigned to the dose level of whichever cohort in Part B (i.e., Cohort 5, 6, 7, or 8) is enrolling at the time these subjects are screened. Subjects who complete Cohorts 1 through 7 of Study 233AS101 (BIIB067 or placebo) will also have the option of switching to a higher dose cohort during or after enrollment in the extension Study 233AS102, at the discretion of the Investigator and according to the criteria specified in Section 7.2.1~~.

~~7.2. Study Specifics~~

~~7.2.1. Cohort Enrollment~~

~~Dose levels will be enrolled sequentially, in an ascending manner, as corresponding dose level cohorts complete Part B of Study 233AS101.~~

~~For each cohort in the extension Study 233AS102, before dosing subjects who enroll after completing Part B of Study 233AS101, the Safety Surveillance Team (SST) will review safety data collected through Day 106 for the corresponding dose level cohort in Study 233AS101. Before the start of the higher dose cohorts, the SST will also review available safety data from the previous cohorts in Study 233AS102. The SST will consist of the Biogen Medical Director, Safety and Benefit-Risk Management (SABR) Physician, and, if required, any ad hoc members. Before dosing the first subject enrolling after completing Part B of Study 233AS101 in each cohort of the extension study, the SST must agree that the current emerging safety and tolerability data support continued exposure for these subjects.~~

~~Subjects who have completed only Part A of Study 233AS101 may be screened for the cohort currently open for enrollment in the extension study.~~

~~Subjects who complete Study 233AS101 (BIIB067 20-60 mg or placebo), may, at the discretion of the Investigator, be switched to a higher dose cohort currently open for enrollment in Study 233AS102. The opening of a higher dose cohort for enrollment in Study 233AS102 will be determined at the planned SST review of emerging safety and tolerability data of the same dose cohort for at least 10 subjects through Day 106 in Study 233AS101. Thus, a favorable SST safety review of BIIB067 60 mg in Study 233AS101 will allow the opening of the 60 mg cohort for those study participants wishing to enroll at this dose in the extension study. Dose switching for a subject may continue up to the highest dose (100 mg), but prior to switching at every level, the planned Day 106 SST review in Study 233AS101 must support dose escalation in the extension study. Furthermore, should a PI wish to escalate the dose level, they must consult with the Sponsor to ensure that current emerging safety and tolerability data support continued exposure for the subject.~~ **will be dosed at 100 mg BIIB067 at their next scheduled Maintenance Dosing Visit**.

**Rationale:** All subjects are allowed to receive 100 mg BIIB067 based on the preliminary findings from Study 233AS101, which showed that all doses including 100 mg were well tolerated and safe; additionally, 100 mg BIIB067 is predicted to be more efficacious than other dose levels. Subjects who have completed Part C of Study 233AS101 are allowed to participate in Study 233AS102 and to continue receiving BIIB067. Because these subjects are already receiving 100 mg BIIB067, they do not need to undergo a washout period and can enter the study sooner, with fewer non-dosing days. However, a blinded loading dose period is needed to preserve the blind in Study 233AS101. Additionally, the deletion of previous text helps avoid confusion about the different dosage forms in Parts A and B of Study 233AS101, as all the subjects enrolled from Part C of Study 233AS102 will be dosed at 100 mg.

This change also affects Section 8.1, Inclusion Criteria (inclusion criterion 7) and Section 9.3, Blinding Procedures.

Section 8, Selection of Subjects

Inclusion and exclusion criteria were updated to align with Part C of Study 233AS101 and as per study requirement.

Section 8.2.1, Inclusion Criteria

**Change:** Inclusion criterion 1 was updated with text related to signing the informed consent by subject or his/her legally authorized representative.

**Now reads:**

1. Ability **of the subject** to understand the purpose and risks of the study and **indicate consent, and ability of the subject or his/her legally authorized representative to** provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations. ~~In the case that a subject is physically incapable of providing informed consent, the subject's legally authorized representative must provide the informed consent.~~

**Rationale:** This change was made to clarify that the subject or his/her legally authorized representative who provided informed consent should understand the purpose and risks of the study and signed the consent according to the requirement of all countries where the study will be conducted.

**Change:** Inclusion criterion 2 was updated to allow subjects who have completed Part C (i.e., final clinic visit) of Study 233AS101 to enroll in Study 233AS102.

**Now reads:**

2. Must have diagnosis of SOD1-ALS, and must have completed ~~Part A and/or Part B~~ **the End of Study Visit for either Parts A, B, or C** of Study 233AS101 (i.e., were not withdrawn ~~and did not miss more than 1 dose of study treatment).~~)

**Rationale:** This change was made to allow subjects who have completed Part C of Study 233AS101 to participate in Study 233AS102 and to clarify the definition of subjects who have completed Part C of Study 233AS101.

**Change:** Inclusion criterion 5, now 6, was updated to remove the requirement that the Sponsor be consulted prior to including subjects with nonclinically significant and stable out-of-range values.

**Now reads:**

~~5.~~**6**. Must have screening values of coagulation parameters including platelet count, international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (APTT) within normal ranges. Coagulation tests may be repeated at the local laboratory once if, in the opinion of the Investigator, values of the initial tests are only slightly out of range. Subjects with nonclinically significant and stable out of range values may be eligible to enroll in the study at the discretion of the Investigator~~,~~ ~~after a consultation with the Sponsor~~. (For normal ranges, please refer to the Study Reference Guide).

**Rationale:** This change was made to align the subject's enrollment requirement with Study 233AS101.

**Change:** Inclusion criterion 6, now 7, was updated with contraception text.

**Now reads:**

~~6.~~**7.** For subjects of childbearing potential must agree to practice effective contraception during the study and **be willing and able to continue contraception** for 5 months after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to (see Section 15.5).

**Rationale:** Text was updated to clarify the contraception requirement of a subject of childbearing potential to willingly continue contraception during the study.

**Change:** Inclusion criterion 8 was updated to clarify that the subjects receiving edaravone as a concomitant medication at study entry must be stable for ≥60 days instead of ≥30 days. Additionally, this inclusion criterion was renumbered from 8 to 4.

**Now reads:**

8.**4.** ~~Subjects taking concomitant edaravone at study entry must be on a stable dose for ≥ 30 days prior to the first dose of study treatment (Day 1) and must continue with the same dose regimen throughout the study, unless the Investigator determines that edaravone should be discontinued for medical reasons, in which case it may not be restarted during the study. Edaravone may not be administered on dosing days during this~~ **If taking edaravone, subject must have initiated edaravone ≥60 days (2 treatment cycles) prior to Day 1. Edaravone may not be administered on dosing days during this** study.

**Rationale:** This change was made to align the edaravone requirement as a concomitant medication with that in Study 233AS101.

This change also affects Section 11.3.1.1, Allowed Concomitant Therapy.

Section 8.2.2, Exclusion Criteria

**Change:** Exclusion criteria 1 and 2, for subjects with a history of human immunodeficiency virus and hepatitis C virus antibody, were deleted.

**Now reads:**

~~1. History of or positive test result for human immunodeficiency virus.~~

~~2. History of, or positive test result at Screening for hepatitis C virus antibody.~~

**Rationale:** Subjects in Study 233AS102 were previously enrolled in Study 233AS101 and were therefore screened for HIV and HCV based on the exclusion criteria for Study 233AS101. There is no requirement in Study 233AS101 that a subject must discontinue study treatment if they acquire HIV or HCV during the course of the study. The requirement for repeat screening is therefore not necessary for patients to roll into Study 233AS102.

Section 11.1, Regimen

**Change:** This section was restructured to clarify how the dosing regimen, including the loading dose, for subjects who have completed Part A or B and subjects who have completed Part C of Study 233AS101 will be handled moving forward and that all subjects will now receive 100 mg BIIB067. Specifically, it was clarified that the loading dose will occur during the first 4 weeks of treatment and that the Maintenance Dose Period will be extended to approximately 58 doses. Details of the prior dosing regimen were removed. Additionally, the time that subjects will be required to stay at the site for safety monitoring following LP was decreased from 6 hours to 1 hour.

**Now reads:**

11.1. Regimen

**11.1.1. Subjects Who Have Completed Parts A or B of Study 233AS101**

Subjects will receive 3 loading doses of BIIB067, approximately 2 weeks apart, ~~and 22~~ **during the first 4 weeks, and up to 58** maintenance doses of BIIB067, approximately every 4 weeks, by IT injection.

- ~~Group 1: 20 mg~~
- ~~Group 2: 40 mg~~
- ~~Group 3: 60 mg~~
- ~~Group 4: 100 mg~~

~~The number of subjects at each dose level will depend on the available subjects diagnosed with SOD1 ALS who complete Part A or Part B of Study 233AS101. Subjects may also have the option of moving to one of the higher dosing cohorts (up to 100 mg) during or after enrollment in Study 233AS102, according to the criteria described in Section 7.2.1.~~

**All subjects who were not receiving the 100 mg dose of BIIB067 will be dosed at 100 mg BIIB067 at their next scheduled Maintenance Dose Visit.**

**11.1.2. Subjects Who Have Completed Part C of Study 233AS101**

**Subjects will not have a washout period. Subjects who received placebo while in Part C of Study 233AS101 will receive 3 loading doses of 100 mg BIIB067 approximately once every 2 weeks (Days 1, 15, and 29), while subjects who received BIIB067 in Part C of Study 233AS101 will receive 2 doses of 100 mg BIIB067, on Days 1 and 29, and placebo on Day 15. All subjects will receive 100 mg BIIB067 at each Maintenance Dose Visit (up to 58 doses) thereafter. Study treatment administered to subjects during the Loading Dose Period is to be blinded.**

**11.1.3. All Subjects**

Prior to injection, approximately 10 mL of CSF will be collected for analyses. Depending on institutional guidelines, anesthesia or sedation may be used for the LP procedure. On dosing days, subjects will remain ~~under observation in~~ **at** the ~~clinic~~ **study site** for ~~approximately 6 hours after~~ **at least 1 hour postdose for safety monitoring and can be discharged at** the ~~LP~~ **discretion of the Investigator and in compliance with the institutional requirements, once the subjects have adequately recovered from the dosing** procedure~~ and~~. **Subjects** will receive a safety follow-up telephone call approximately 24 hours after the procedure. During the follow-up periods, subjects will remain under observation in the clinic for approximately 1 hour after the LP procedure and will receive a safety follow-up telephone call approximately 24 hours after the procedure. Refer to and follow the Directions for Handling and Administration (DHA).

11.2. Modification of Dose and/or Treatment Schedule

The dosage should not be modified, other than as stated in Section 7.2.**2**. ~~However, if necessary (e.g., dose is not tolerated), after review of all available data by the Biogen Medical Director, a~~

~~SABR Physician, the Primary Investigator, and, if required, any ad hoc members, an alternative dose or dosing regimen may replace the planned dose or dosing regimen for the subsequent cohort.~~ Any change in the planned dose or dosing regimen would require a protocol amendment.

**Rationale:** All subjects will now receive 100 mg BIIB067, so this information is no longer applicable. The requirements of lumbar puncture postdose safety monitoring are aligned with those of Study 233AS101.

[redacted]

Section 15.5, Contraception Requirements

**Change:** Contraception requirements were updated.

**Now reads:**

All women of childbearing potential ~~and all men~~ must ~~practice~~ **ensure that** effective contraception **is used** during the study and for 5 months**, whichever is longer,** after their last dose of study treatment. In addition, ~~male~~ **female** subjects should not donate ~~sperm~~ **eggs** for the duration of the study and for at least 5 months after their last dose of study treatment.

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

- Postmenopausal
  - 12 **continuous** months of natural (spontaneous) amenorrhea without an alternative medical cause and a serum follicle-stimulating hormone **(FSH)** level >40 mIU/mL

  - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
  - Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, ~~highly~~ effective contraception is defined as use of **1 of** the following:

For females:

- Established use of oral, injected, ~~or~~ implanted**, intravaginal, or transdermal** hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine **hormone-releasing** system.
- ~~Male~~ **Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.**
- **Sex with a male who has undergone** surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate). ~~(For female subjects participating in the study, male sexual partners must have undergone surgical sterilization.)~~

~~For males:~~

- ~~A vasectomy with negative semen analysis at follow up.~~
- True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

**Rationale:** Contraception requirements were updated to reflect the availability of reproductive toxicology study results.

Section 16.1, Clinical Function

**Change:** Text related to the method of PD analysis for all subjects was updated, and text for subjects who have completed Parts A and B of Study 233AS101 and Part C of Study 233AS101 was clarified.

**Now reads:**

16.1. Clinical Function

16.1.1. Analysis Population

The clinical function~~/PD~~ population is defined as subjects who have received at least 1 dose of study treatment and have at least 1 available postdosing evaluation of the respective clinical function ~~or PD~~ endpoint in the extension study.

~~In the analysis, for subjects who switched dose cohort during the study, an "intent-to-treat" principle will be employed to assign dose cohorts for those subjects; that is, subjects will always be assigned to their initial dose cohort when they started the study.~~

16.1.2. Methods of Analysis

~~Because~~ **As** this is an open-label, ~~uncontrolled study, all clinical function endpoints will be evaluated either in reference to historical placebo data or based on observed changes in the longitudinal trajectory. All~~ **long-term extension study,** analyses will be exploratory **and descriptive** in nature~~, and no formal statistical testing will be performed.~~ .

Data will be summarized ~~by dose level~~ using descriptive statistics ~~(N, mean, standard deviation [SD], median, minimum, and maximum)~~ for continuous variables and using frequency and percentage for discrete variables. **For subjects who have completed Parts A or B of Study 233AS101, the time trajectory of each clinical function and PD variable may be summarized for the period of each dose level. For subjects who have completed Part C of Study 233AS101, the time trajectory will be summarized by the prespecified mutation/progressing group (fast-progressing versus non-fast-progressing) and the treatment received during Study 233AS101 from the baseline of Study 233AS101 (including data from Studies 233AS101 and 233AS102), from the baseline of Study 233AS101 (including data from Study 233AS102 only), and from the start of BIIB067 100 mg dosing.**

Disease progression will be measured based on changes in ALSFRS-R, SVC, [redacted]**-HHD,** [redacted]~~, HHD,~~ [redacted]. The ~~improvement in ALSFRS-R is defined as the positive estimated~~ **linear mixed model for repeated measures (MMRM) will be used to assess the** slope of ~~ALSFRS-R~~ **change by mutation/progressing group (fast-progressing versus non-fast progressing) and the treatment received during Study 233AS101. Baseline characteristics at the start of Study 233AS101 may be included as fixed covariates. The slope of ALSFRS-R score change will be estimated using linear MMRM as well as derived** using data points from each individual participant~~, based on assumed linear declining of ALSFRS-R. The proportion of positive slope will be estimated and presented along with the 95% CI~~ **for each 48-week period. Categorical analysis of slopes in different ordered categories may also be performed**.

~~We postulate that an improvement in disease progression can be demonstrated in subjects with an observed PD effect of BIIB067, defined as a reduction in total CSF SOD1 protein by at least 25%. The effect of dose level and other covariates including, but not limited to, gender, disease onset site, riluzole and edaravone use, and the total number of active doses and the dosing gap prior to the extension study, may be explored using statistical modelling.~~ **VAFS and overall survival will be summarized using Kaplan-Meier curves based on the starting time using the following:**

1. **Entry into Study 233AS101**

2. **Entry into Study 233AS102**
3. **The start of BIIB067 100 mg dosing**

The relationship between PK or PD endpoints and the clinical function endpoints will also be explored.

**Rationale:** This change was made to clarify that difference between the time trajectories of subjects who participated in Parts A and B of Study 233AS101 and those who participated in Part C of Study 233AS101. Subjects who completed Parts A and B of Study 233AS101 received different dosages prior to Version 4 of Protocol 233AS102, whereas all subjects who completed Part C of Study 233AS101 will receive a 100 mg BIIB067 dose in Study 233AS102. Hence, the analysis is different among the subjects enrolling from different parts of Study 233AS101 into Study 233AS102.

This change also affects Section 16.3.2, Methods of Analysis (for PD endpoints).

Section 16.6, Interim Analyses

**Change:** Interim analysis was added.

**Now reads:**

~~16.5.~~**16.6.** Interim Analyses

~~No formal interim analysis is planned for this study.~~

**Interim analyses may be performed periodically to provide content for regulatory submissions and safety updates and to support drug development planning and business activities.**

**Rationale:** Interim analyses were added to support regulatory submissions and further drug development planning and business activities.

Section 16.7, Sample Size Considerations

**Change:** Study's subject sample size was increased from 84 subject to 144 subjects.

**Now reads**:

~~16.6.~~**16.7.** Sample Size Considerations

The sample size for this study is based on the ~~sample size~~ number of the SOD1-ALS ~~population~~ **subjects** in Study 233AS101 **who consent to participate**. Up to ~~approximately 84~~ **144** subjects will be dosed in Study 233AS101.

**Rationale:** The study sample size was increased because subjects who participated in Part C of Study 233AS101 will be allowed to participate in this open-label extension Study 233AS102.

Section 19.2, Study Committees

**Change:** Added an independent data monitoring committee (IDMC) and removed the reference to the Safety Surveillance Team (SST).

**Now reads:**

~~19.2.1. Safety Surveillance Team~~

~~An SST, as described in Section 7.2.1, will monitor dose escalation and the opening of extension cohorts. The SST will meet to review safety data at least every 3 months, and more frequently as needed.~~

19.2.1. **Independent Data Monitoring Committee**

**An IDMC will be formed to review ongoing safety and tolerability data. Members of the IDMC will not be allowed to participate as Investigators in this study. The IDMC will review safety data on an ongoing basis to ensure the safe and proper treatment of subjects. Regular IDMC meetings will occur approximately every 3 months after the first meeting. An IDMC charter will provide full guidance on the function and practices to be followed by the IDMC.**

**Rationale:** The IDMC will review safety data on an ongoing basis to ensure the proper treatment of subjects and to maintain the blind in pivotal Study 233AS101 (Part C). The reference to the SST was removed because it is no longer applicable.

This change also affects Section 7.4, Study Stopping Rules.

# SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- The Sponsor signatory was updated.
- Details of Biogen Japan were added as a Sponsor.
- Section 2, List of Abbreviations, was updated.
- Section 5, Introduction, a description of the mechanism of action information for BIIB067 from the Investigator's Brochure was added.
- Section 5.3.2, Clinical Experience, a statement that additional information on the preliminary efficacy, safety, pharmacokinetics, and pharmacodynamics for BIIB067 can be found in the Investigator's Brochure was added.
- Section 7.1, Study Overview, Japan was added as an additional country for potential sites in order to enable eventual filing for Japan.
- Section 7.3, Study Stopping Rules, previously Section 7.4, and text related to AEs were modified with unexpected and serious unacceptable risks.
- Section 7.4, End of Study, previously Section 7.5, and the end of study requirements were updated for clarity because the study has been extended to 2 years.
- Section 8.2, Exclusion Criteria, criteria 1 previously 3, text updated as per Study 233AS101.
- Section 8.2, Exclusion Criteria, and Section 11.3.1.2, Disallowed Concomitant Therapy, aspirin was removed as an excluded concomitant medication.
- Section 10.1, Discontinuation of Study Treatment, text was updated about the subjects who discontinue study treatment and who terminate from the study early.
- Section 11.2, Modification of Dose and/or Treatment Schedule, text was added to clarify that dose modification requirements are not allowed because there is only one dose (Cohort) of 100 mg allowed in this study.
- Section 11.3.1.1, Allowed Concomitant Medication, text related to concomitant medication (riluzole and edaravone) was updated to permit the subjects to remain on a stable dose until the completion of Week 12 Visits or as per Investigator's discretion.
- Section 12.1, BIIB067, label description was updated to align with Study 233AS101.
- Section 12.2 Placebo Product, a new subsection was added to provide details of the placebo used in the study during the Loading Dose Period for subjects who are enrolling in this study from Part C of Study 233AS101.

- Section 13.1.1, ALS Functional Rating Scale-Revised, text was added to clarify that the site staff who performed ALSFRS-R are to remain blind for other study procedures until the end of the Loading Dose Period.
- Section 13.3, Pharmacodynamic Assessments, [redacted] urine collection were added.
- Section 14.2, Laboratory Safety Assessments, laboratory assessments were updated for clarity. Neutrophil count was deleted from hematology because it is covered in complete blood count, and electrolytes were deleted from the blood chemistry list.
- Section 15.1.2, Serious Adverse Events, text was updated to classify a medically important event as a serious adverse event (SAE).
- Section 15.3.1, Adverse Events, text was added to clarify that at each study visit, the Investigator will assess the subject's adverse events (AEs) and record any new AEs or updates to previously reported AEs.
- Section 15.3.3, Immediate Reporting of Serious Adverse Events, "Reporting Information for SAEs" text was updated to remove text stating that any SAE between consent and last Follow-Up Visit must be reported within 24 hours and that thereafter, events should only be reported if they are related to study treatment.
- Section 15.4.1, Pregnancy, text was added to clarify that a pregnancy is not considered an AE and should not be recorded as such and that pregnancy can also be reported via email.
- Section 15.4.2, Overdose, and Section 15.6.1, the Investigator, text was added indicating that overdose and SAEs may be reported by email.
- Section 16.3.2, Method of Analysis, text was added to clarify that the analysis of PD variables will be performed using a similar method to that used for clinical function.
- [redacted]
- Section 16.5.2.4, Columbia Suicide Severity Rating Scale, previously Section 16.4.2.4, text was modified for clarity.
- Section 16.4.2.5, Physical Examination, the subsection was deleted.
- Section 16.5.2.1, Adverse Events, the methods of analysis of AEs text was updated to include SAEs, deaths, and AEs leading to discontinuation, which will be summarized by time interval on given dose levels. In addition, the incidence rate per person year will be determined along with Kaplan-Meier estimates of survival.
- The vendor information was updated to Sponsor information throughout (changed from "[redacted]" to "Biogen").
- Section 20, References, 2 references were deleted from the list: Rutkove 2014 and Rutkove 2012.

- Typographical errors and formatting were corrected.

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# AMENDMENT SUMMARY

Biogen Protocol 233AS102

An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation

Version 3

Date: 12 March 2018

EUDRA CT Number: 2016-003225-41

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

## PRIMARY REASON FOR AMENDMENT

The primary reasons for this amendment to Protocol 233AS102 are to extend the treatment period by 12 months for all patients in the study, and to add a fourth treatment group of BIIB067 100 mg.

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

Section 7.1, Study Overview

**Now reads:**

In Study 233AS101, the Investigators, study staff (except for a designated pharmacist/technician), and study subjects are blinded to the randomized study treatment assignments. To preserve the blinding used in Study 233AS101 until database lock, subjects in Study 233AS102 will have a washout period of at least 4 times the t½ (~16 weeks) from the time of their last dose of study treatment in Study 233AS101 to their first dose in Study 233AS102. Subjects will receive 3 loading doses of BIIB067, approximately 2 weeks apart, during the first ~~month~~ **4 weeks** and ~~10~~ **22** maintenance doses, approximately ~~monthly~~**every 4 weeks**, by IT injection.

**Rationale:** The purpose of extending the treatment period by 12 months is to allow a longer period of treatment exposure for studying the long-term effects of exposure to BIIB067.

This change also affects Sections 4.1, Study Schematic; 4.2, Schedule of Activities; 7.3, Overall Study Duration and Follow-Up; and 7.5, End of Study.

**Now reads:**

**Initial** ~~D~~**d**ose level assignment for each subject ~~that~~**who** completes Part B of Study 233AS101 will correspond to their cohort assignment in Study 233AS101, regardless of whether they received BIIB067 or placebo. All subjects randomized to Cohort 5 (BIIB067 20 mg or placebo) in Study 233AS101 will receive BIIB067 20 mg; subjects who were randomized to Cohort 6 (BIIB067 40 mg or placebo) will receive BIIB067 40 mg, ~~and~~ those randomized to Cohort 7 (BIIB067 60 mg or placebo) will receive BIIB067 60 mg**, and those randomized to Cohort 8 (BIIB067 100 mg or placebo) will receive BIIB067 100 mg**. If the highest dose (~~60~~ **100** mg) is dropped based on results from the multiple ascending dose (MAD) portion (Part B) of Study 233AS101, subjects in Cohort ~~7~~ **8** will be placed in the ~~40~~ **60** mg cohort ~~(Cohort 6)~~**in this extension study**.

**Rationale:** Achieving maximum efficacy in the treatment of superoxide dismutase 1 (SOD1) amyotrophic lateral sclerosis (ALS) is likely dependent on reducing the levels of the toxic, mutant version of SOD1 throughout the central nervous system (CNS), including the brain

(motor cortex) and spinal cord. Emerging preliminary pharmacokinetic data from Study 233AS101 indicate that the exposure to BIIB067 was less than that predicted preclinically. The purpose of adding a higher-dose cohort (100 mg) to Study 233AS101, and subsequently to extension Study 233AS102, was to enable a higher exposure to BIIB067, which would more effectively reduce SOD1 in the CNS, and is supported by the safety margins from the 9-month nonhuman primate (NHP) study. The extension study aims at studying the long-term effects of exposure to BIIB067 100 mg.

This change also affects Sections 7.3.1, Screening; 11.1, Regimen; and 16.6, Sample Size Considerations.

## SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 3, Synopsis

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

Section 4.2, Table 1: Schedule of Activities

**Change:** Visit dates for Maintenance Dose Visits and Follow-Up Visits are now presented as days as well as months. In addition, the second and third loading dose visits were changed to take place on Days 15 and 29, and the anti-BIIB067 antibody sampling was removed from the Screening Visit.

**Now reads:**

| | Screening Visit [1] | Baseline/1st Loading Dose Visit | 2nd Loading Dose Visit | 3rd Loading Dose **Visit** | Maintenance Dose Visits | Follow-Up Visits | Final/ Early Termination Visit |
|---|---|---|---|---|---|---|---|
| Assessments | Day -28 to Day -1 | Day 1 | Day ~~14~~**15** (±3 days) | Day ~~28~~**29** (±3 days) | **Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, & 645** ***(i.e.,*** *Months 3-~~12~~**24)*** (±3 days) | **Days 673 & 701** ***(i.e.,*** *Months ~~13~~**25** & ~~14~~**26)*** (±7 days) | Day ~~393~~**729** *(i.e., Month ~~15~~**27**)* (±7 days) |

**Rationale:** These changes permit more precision in scheduling visits.

These changes also affect Sections 4.1, Study Schematic; 7.3.2, Dosing; 7.3.3, Follow-Up; and 11.3.1, Concomitant Therapy.

**Now reads:**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Blood Samples for Plasma anti-BIIB067 Ab | ~~X~~ | X[5] | X | X[5] | X[5] | | X |

**Rationale:** Removing anti-BIIB067 antibody sampling from the Screening Visit will help prevent unnecessary procedures at this visit.

This change also affects Section 4.1, Study Schematic.

Section 5.2, Current Therapies for Amyotrophic Lateral Sclerosis

**Change:** Included information on edaravone as a current therapy for ALS.

**Now reads:**

The only currently approved treatment**s** for ALS ~~is~~ **are** ~~Rilutek® (~~riluzole~~)~~ **(Rilutek®) which is marketed globally, and edaravone (Radicava™), which is approved in the United States, Japan, and South Korea. Riluzole** ~~which~~ provides a modest increase in survival (2 to 3 months) without noticeable improvement in strength or disability [Miller 2012]. **Edaravone lessens functional decline as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R). The effect of edaravone on survival is unknown [Writing Group and Edaravone (MCI-186) ALS 19 Study Group 2017]**. No specific treatments for SOD1-ALS are available.

**Rationale:** This change was made because edaravone was recently approved as a treatment for ALS.

Section 5.3.1.1, Toxicology

**Change:** Added description of a 9-month nonclinical toxicology study in cynomolgus monkeys (NHPs).

**Now reads:**

**From the 9-month cynomolgus monkey toxicology study, the NOAEL for repeated, IT-administered BIIB067 was 12 mg. This was based on adverse clinical observations for 1 female administered 35 mg. This female exhibited neurological signs after the second dose, characterized by transient muscle cramping (seen immediately after dosing on multiple days), prolonged recovery from anesthesia, and intermittent tremors (during the last months of the dosing phase). Treatment with diazepam was required on several dosing occasions. An electroencephalogram (EEG) on this animal revealed altered postdose signals (with effects on high frequency bands) but confirmed that muscle cramping during EEG recording was not a seizure and could have been related to arousal. This finding was considered test-article related; however, there were no correlates in clinical and anatomic pathology.**

**Rationale:** A long-term nonclinical toxicology study was recently completed to support clinical development of BIIB067, and the data generated in NHPs were used to update the dosing rationale in the first-in-human study of BIIB067.

This change also affects Section 5.3.1, Nonclinical Experience.

Section 5.5, Rationale for Dosing Regimen

**Change:** The dosing rationale was updated to include the 100-mg dose of BIIB067.

**Now reads:**

The BIIB067 dosing regimens for Study 233AS101 were selected based on target tissue concentrations from SOD1 transgenic mouse models, and nonclinical toxicology and PK observations in repeated dose, **IT administration in** 13-week **and 9-month** nonhuman primate (NHP) studies.

**Based on pharmacology and PK results in SOD1 transgenic mice, the estimated tissue concentrations of BIIB067 needed to produce a 50%, and the upper 95% confidence interval (CI) of an 80%, SOD1 mRNA reduction within the human spinal cord are 0.9 µg/g and 4.7 µg/g, respectively. Evaluations of cortex from the same experiment indicate that the estimated tissue concentration of BIIB067 needed to produce a 50% cortical SOD1 mRNA reduction is 8 µg/g.**

**The lowest dose selected for Study 233AS101 (10 mg) was predicted to achieve greater than 0.9 µg/g tissue concentration in the spinal cord. The initial highest proposed dose (60 mg, multiple dose) was predicted to achieve greater than 4.7 µg/g steady-state tissue concentration in the spinal cord, and approximately 1.5 µg/g steady-state tissue concentration in the cortex, which is expected to yield approximately 15% to 20% SOD1 mRNA reduction in that tissue. The addition of a 100 mg cohort is predicted to achieve steady-state exposures in the cortex of approximately 2.5 µg/g, which is predicted to be sufficient for a meaningful CSF SOD1 reduction of 25% to 30%. This reduction is expected to be clinically meaningful, based on the expectation that the reduction of SOD1 in tissues (spinal cord and cortex) would be greater than the 20% to 30% reduction observed in CSF. This prediction is based on observations in NHP studies, where approximately 50% reduction in CSF corresponded to approximately 50% or greater reduction in the spinal cord and cortex. In rodent efficacy experiments, doses of BIIB067 that reduced tissue SOD1 by approximately 30% or more were found to improve measures of electrophysiology, function, and neurofilament.**~~The FIH dose was calculated using the 50% of maximum observed biologic effect value for SOD1 mRNA reduction following intracerebroventricular administration of BIIB067 in the SOD1-G93A mouse. The monkey whole body physiologically based PK model was scaled to humans using a 10× scaling factor, based both on the human:NHP ratio of CSF fluid volumes and on the ratio of the CSF turnover rate.~~

~~The highest BIIB067 dose (60 mg) is predicted to achieve greater than the upper 95% confidence interval (CI) of an 80% SOD1 mRNA reduction within the human spinal cord.~~

**Based on nonclinical PK and pharmacology data, and taking into consideration subject safety, the inconvenience of repeated IT injections, and the rapid, fatal nature of ALS, the following dose intervals were selected for this extension study: 3 loading doses, once every 2 weeks, and 22 maintenance doses, administered approximately every 4 weeks from Months 3 to 24. These intervals were selected based on the estimated t½ of BIIB067 (~1 month) in the target CNS tissues (spinal cord and brain cortex), to achieve and maintain the target tissue concentration of BIIB067 at a steady-state level and within the estimated pharmacologically active range, and allow collection of PK and pharmacodynamic (PD) data during dose interruption and resumption, providing information on the dynamic behavior of the system.**

**From the 9-month NHP toxicology study, the NOAEL for repeated, intrathecally administered BIIB067 was 12 mg. This NOAEL was converted to a human equivalent dose (HED) based on the NHP to human CSF volume scaling (approximately 10-fold difference). CSF volume scaling conservatively estimates the needed scaling factor and has predicted HED with reasonable accuracy. The HED for the 9-month, intrathecal NHP toxicology study was calculated to be 120 mg. This provides a 6-fold safety margin for the BIIB067 starting dose (20 mg) of the extension study, and a 2-fold safety margin for the 60 mg dose. The safety margin for a 100 mg clinical dose (highest planned dose) would be 1.2-fold. Preliminary PK data (plasma area under the concentration time curve [AUC] from time 0 to 24 hours) from the 20 mg MAD cohort in Study 233AS101, indicate that the safety margin based on exposure is 2.2-fold relative to a 100 mg clinical dose. The 1.2-fold safety margin based on CSF volume scaling from the NHP toxicology study was chosen over the 2.2-fold safety margin calculated from the plasma steady-state exposures, since the former provides a more conservative estimate.**

**Therefore, all BIIB067 doses planned for Studies 33AS101 and 233AS102 are predicted to be pharmacologically active, while maintaining sufficient safety margins calculated from the 9-month IT NHP toxicology study.**

**Rationale:** This change was made based on BIIB067 exposure predictions related both to the addition of the 100-mg dose and to updated information from the 9-month NHP toxicology study. The human equivalent dose and the safety margin relative to the new highest planned dose of 100 mg were also included.

Section 6.1, Primary Objectives and Endpoints

**Change:** Deleted laboratory assessments, vital signs, and physical examinations from the primary endpoint.

**Now reads:**

The associated primary endpoints are the incidence of AEs and serious adverse events (SAEs)~~, and incidence of abnormalities in clinical laboratory assessments, vital signs, physical and neurological examinations, and electrocardiograms (ECGs)~~.

**Rationale:** Any clinically significant abnormal values collected for the deleted assessments will be captured as AEs for reporting purposes, making the inclusion of these assessments as endpoints unnecessary.

Section 7.1, Study Overview

**Change:** The number of sites participating in this study was decreased to 16.

**Now reads:**

This is a multicenter, open-label, uncontrolled, extension study to assess the long-term safety, tolerability, PK, and effect on disease progression of BIIB067 administered by IT injection to previously treated subjects with SOD1-ALS who have completed Part A and/or Part B of Study 233AS101. The study will be conducted at approximately ~~17~~ **16** sites in the United States, Canada, and Western Europe.

**Rationale:** Italy was removed as one of the participating sites in this study.

Section 7.2.1, Cohort Enrollment

**Change:** Changes were made describing the process for subjects switching to a higher-dose cohort.

**Now reads:**

~~In addition, s~~**S**ubjects who have completed only Part A of Study 233AS101 may **be screened for the cohort currently open for enrollment in the extension study**~~also be eligible to participate in Study 233AS102. Part A only participants may be screened for inclusion in the currently enrolling cohort of Study 233AS102 after at least 3 subjects in the corresponding dose level cohort in Part B of Study 233AS101 have received a cumulative dose of BIIB067 greater than or equal to the sum of the dose which the subject being screened received in Part A of Study 233AS101 and the first dose that this subject will receive in Study 233AS102. (For example, a subject who received a 20 mg dose of BIIB067 in Part A of Study 233AS101 may be eligible to enroll into the 40 mg dose cohort of Study 233AS102 after at least 3 subjects in the 40 mg dose cohort in Part B of Study 233AS101 have received a cumulative dose of at least 60 mg of BIIB067.) Prior to enrollment of the first Part A subject in any 233AS102 cohort, the SABR Physician must review the Study 233AS101 Part B exposure up to that time to ensure this criterion has been met~~.

**Subjects who complete Study 233AS101 (BIIB067 20-60 mg or placebo), may, at the discretion of the Investigator, be switched to a higher dose cohort currently open for enrollment in Study 233AS102. The opening of a higher dose cohort for enrollment in Study 233AS102 will be determined at the planned SST review of emerging safety and tolerability data of the same dose cohort for at least 10 subjects through Day 106 in Study 233AS101. Thus, a favorable SST safety review of BIIB067 60 mg in Study 233AS101 will allow the opening of the 60-mg cohort for those study participants wishing to enroll at this dose in the extension study. Dose switching for a subject may continue up to the highest dose (100 mg), but prior to switching at every level, the planned Day 106 SST review in Study 233AS101 must support dose escalation in the extension study. Furthermore, should a PI wish to escalate the dose level, they must consult with the Sponsor to ensure that current emerging safety and tolerability data support continued exposure for the subject.**

**Rationale:** Enabling subjects to switch to a higher dose would allow them to attain higher exposure levels of BIIB067 within acceptable safety and tolerability limits, and possibly more effective treatment. It would also provide long-term PK and PD data on the exposure-response relationship and the dynamic effects of this system.

This change also affects Sections 16.1.1, Analysis Population; 16.1.2, Methods of Analysis (Clinical Function); and 16.3.2, Methods of Analysis (Pharmacodynamics).

Section 8.1, Inclusion Criteria

**Change:** An eligibility criterion was added specifying the 16-week washout prior to the subject's first dose in this study. In addition, an eligibility criterion was updated to permit the use of edaravone provided it is not administered on dosing days.

**Now reads:**

**7. Must have a washout ≥16 weeks between the last dose of study treatment received in Study 233AS101 and the first dose of BIIB067 received in the current Study 233AS102.**

**Rationale:** This change was made for clarity. Although the current washout period prior to the first dose of BIIB067 in Study 233AS102 was already 16 weeks, it was not explicitly stated as an inclusion criterion. The washout period is now noted as an inclusion criterion for the study.

**Now reads:**

~~6.~~**8. Subjects taking concomitant edaravone at study entry must be on a stable dose for ≥ 30 days prior to the first dose of study treatment (Day 1) and must continue with the same dose regimen throughout the study, unless the Investigator determines that edaravone should be discontinued for medical reasons, in which case it may not be restarted during the study. Edaravone may not be administered on dosing days during this study.**

**Rationale:** Edaravone was recently approved as a treatment for ALS in the United States, Japan, and South Korea, and was added as a permitted medication during this trial.

This change also affects Sections 11.3.1.1, Allowed Concomitant Therapy; and 16.1.2, Methods of Analysis (Clinical Function).

Section 8.2, Exclusion Criteria

**Change:** Updates were made to the exclusion criteria for hepatitis C- and B. In addition, presence of implanted venous devices was added as an exclusion criterion.

**Now reads:**

2. History of, or positive test result **at Screening** for hepatitis C virus antibody ~~or hepatitis B virus (defined as positive for both hepatitis B surface antigen and hepatitis B core antibody)~~.

~~2.~~**3. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive hepatitis B surface antibody immunoglobulin G, and positive HBcAb) or vaccination (defined as positive anti-HBs) are eligible to participate in the study.**

**Rationale:** This update is to clarify the timing for the hepatitis C antibody test and to provide a more detailed definition for hepatitis B exclusion criteria.

**Now reads:**

~~8.~~**10. Presence of an implanted intravenous port/catheter.**

**Rationale:** This change was made to avoid risks associated with implanted venous devices, including infection.

Section 14.1, Clinical Safety Assessments

**Change:** The types of neurological examinations to be conducted at study sites were added.

**Now reads:**

- **Limited** ~~N~~**n**eurological examinations~~,~~ **(to be assessed by a trained specialist) of cranial nerves, coordination/cerebellar function, reflexes, motor, and** ~~including the~~ Mini-~~mental~~**Mental** State Examination **(MMSE; a 30-point questionnaire that is used to measure cognitive impairment** ~~(to be assessed by a trained specialist~~)

**Rationale:** This change will eliminate confusion and enable consistency in the type of neurological examinations performed across study sites.

This change also affects Sections 4.2, Schedule of Activities; and 16.4.2.6, Limited Neurological Examinations.

Section 14.2, Laboratory Safety Assessments

**Change:** Coagulation assessments were separated from other hematology assessments.

**Now reads:**

- Hematology: Complete blood count withdifferential and platelet count, and absolute neutrophil count. Platelet count~~, INR, PT, and APTT~~ will also be measured for all subjects at Screening and at all dosing and follow-up visits~~.~~

- **Coagulation: INR, PT, and APTT (all of which will also be measured for all subjects at Screening and at all dosing and follow-up visits)**

**Rationale:** This change was made for clarity, since coagulation is not part of the standard hematology assessments.

This change also affects Sections 4.2, Schedule of Activities; and 16.4.2.2, Clinical Laboratory Results.

Section 17.3, Subject Information and Consent

**Change:** Text was added stating that subjects will be informed about the collection of race and ethnicity data.

**Now reads:**

Subjects will be informed that their race and ethnicity will not be collected for the purposes of data analysis during the **extension** study. **However, this information was collected in Study 233AS101, where applicable and after subject consent, unless the collection was not permitted by applicable law or not approved by the governing ethics committee, and the data will be used during analysis of the results of that study.** ~~In addition, subjects who have the capacity should provide their assent to participate in the study. The level of information provided to subjects should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.~~

**Rationale:** This update was made to clarify informed consent and the use of race and ethnicity data for subjects participating in Studies 233AS101 and 233AS102.

## SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- On the title page, the Sponsor address in the United States was updated.
- The signatory's title was updated.
- The List of Abbreviations was updated.
- In Section 4.1, Figure 1, Study Schematic was replaced to correct minor errors.
- In Section 13.2, Pharmacokinetic Assessments the use of abbreviations was corrected to include the abbreviation definition.
- The [redacted] assessment was updated to [redacted] to clarify the version to be used.
- The term "monthly" was changed to "every 4 weeks" throughout.
- The term "study drug" was changed to "study treatment" per Biogen style.
- A new reference was added to the Reference list.
- Formatting and typographical errors were corrected.

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# AMENDMENT SUMMARY

Biogen Protocol 233AS102

An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation

Version 2

Date: 21 April 2017

EUDRA CT Number: 2016-003225-41

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

## PRIMARY REASON FOR AMENDMENT

The primary reasons for this amendment to Protocol 233AS102 are 1) to eliminate the requirement to review data from Day 106 through Day 169 of Study 233AS101 before dosing the first and second subject enrolling in each cohort of Study 233AS102, and 2) to clarify criteria for enrolling subjects who complete only Part A of Study 233AS101.

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

Section 7.2.1, Dose Escalation/Opening of Extension Cohorts

**Now reads:**

**7.2.1** ~~Dose Escalation/Opening of Extension Cohorts~~ **Cohort Enrollment**

Dose levels will be enrolled sequentially, in an ascending manner, as **corresponding dose level** cohorts complete Part B of Study 233AS101 ~~and become eligible for screening into the extension study~~.

~~Prior to beginning~~ **For** each cohort~~'s dosing~~ in the extension ~~s~~**S**tudy **233AS102, before dosing subjects who enroll after completing Part B of Study 233AS101,** the Safety Surveillance Team (SST) will review safety data **collected through Day 106** for the corresponding dose **level** cohort ~~for all subjects contributing to the dose escalation safety data through Day 106 of~~ **in** Study 233AS101~~, as well as the additional safety data for the first subject reaching the Day 169 time point~~. **Before the start of the higher dose cohorts, the SST will also review available safety data from the previous cohorts in Study 233AS102.** The SST will consist of the Biogen Medical Director, Safety and Benefit-Risk Management (SABR) Physician, Biostatistician, Clinical Pharmacologist, and, if required, any ad hoc members. ~~If after reviewing the safety data for the first subject~~ **Before dosing the first subject enrolling after completing Part B of Study 233AS101** in ~~the~~ **each** cohort **of the extension study**, the SST **must** agree~~s~~ that the current emerging safety and tolerability data support ~~opening the cohort, then the subject can continue into the extension study~~ **continued exposure for these subjects**.

In addition, ~~at this time,~~ subjects who have completed **only** Part A of Study 233AS101 may also be ~~screened for inclusion~~ **eligible to participate** in Study 233AS102. ~~In Study 233AS101, each cohort will be randomized in blocks of 4 (3 active, 1 placebo). Therefore, the SST will also review any additional safety data for the second subject to complete Study 233AS101 during study Days 106 to 169, before allowing the remainder of the cohort to continue into Study 233AS102. This timeframe will allow for safety assessment in the event that the first subject received placebo. If the first and second subjects reach Day 169 within 2 weeks of one another, the SST may have one meeting to review the data for both subjects. Before the start of the higher dose extension cohorts, the SST will also review available safety data from the previous cohorts in Study 233AS102.~~ **Part A-only participants may be screened for inclusion in the currently enrolling cohort of Study 233AS102 after at least 3 subjects in the corresponding dose level cohort in Part B of Study 233AS101 have received a cumulative dose of BIIB067 greater than or equal to the sum of the dose which the subject being screened received in Part A of Study 233AS101 and the first dose that this subject will receive in**

**Study 233AS102. (For example, a subject who received a 20-mg dose of BIIB067 in Part A of Study 233AS101 may be eligible to enroll into the 40-mg dose cohort of Study 233AS102 after at least 3 subjects in the 40-mg dose cohort in Part B of Study 233AS101 have received a cumulative dose of at least 60 mg of BIIB067.) Prior to enrollment of the first Part A subject in any 233AS102 cohort, the SABR Physician must review the Study 233AS101 Part B exposure up to that time to ensure this criterion has been met.**

**Rationale:** Emerging safety and tolerability data from the ongoing Study 233AS101 have been favorable, making the lengthy follow-up for the first subjects enrolling in each cohort of the extension study unnecessary. This change will decrease the wait time between the last dose in Study 233AS101 and the first dose in extension Study 233AS102 for affected subjects.

Edits to the text describing criteria for enrolling subjects who complete only Part A of Study 233AS101 were made for clarity, in response to feedback from study sites.

## SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Section 9.1, Screening and Enrollment

**Change:** A condition under which subjects may be rescreened was added.

**Now reads:**

Subjects (or their legally authorized representative [e.g., spouse], where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the informed consent form (ICF), that subject is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

**Eligible subjects who are not able to complete the Day 1 Visit within 28 days of starting their screening assessments may be rescreened.**

**Rationale:** This change will allow eligible subjects who could not, for logistical reasons, complete the Day 1 Visit in time an opportunity to rescreen.

## SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- The Sponsor Signature information was updated.
- Minor grammatical errors were corrected.