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Official Title:	A Phase 1/2 Multiple-Ascending-Dose Study With a Long-Term Open-Label Extension to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Effect on Disease Progression of BIIB105 Administered Intrathecally to Adults With Amyotrophic Lateral Sclerosis With or Without Poly-CAG Expansion in the ATXN2 Gene
NCT Number:	NCT04494256
Document Date:	07 September 2023

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PROTOCOL NUMBER: 275AS101

PHASE OF DEVELOPMENT: 1/2

PROTOCOL TITLE: A Phase 1/2 Multiple Ascending Dose Study With a Long-Term Open-Label Extension to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Effect on Disease Progression of BIIB105 Administered Intrathecally to Adults With Amyotrophic Lateral Sclerosis With or Without PolyCAG Expansion in the *ATXN2* Gene

EUDRA CT NUMBER: 2020-000207-36

IND NUMBER: 145541

DATE: 07 September 2023
Version 5
FINAL
Supersedes previous Version 4 dated 09 September 2022

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SPONSOR INFORMATION

This study is a partnership between Biogen and IONIS. Biogen is responsible for the study.

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

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Date (*DD MMM YYYY*)

TABLE OF CONTENTS

SPONSOR INFORMATION 2
SPONSOR SIGNATURE PAGE 3
TABLE OF CONTENTS 4
LIST OF TABLES 9
LIST OF FIGURES 9
1. KEY STUDY ELEMENTS 10
1.1. Synopsis 10
Study Design Schematic 26
Schedule of Activities 27
2. LIST OF ABBREVIATIONS 50
3. INTRODUCTION 52
3.1. Study Rationale 52
3.1.1. Rationale for Study Population 53
3.1.2. Rationale for Starting Dose and Maximum Exposure 53
3.1.3. Rationale for the Collection of Genetic Samples 55
3.2. Background 56
3.2.1. Overview of ALS 56
3.2.2. Current Therapies for ALS 56
3.2.3. Profile of Previous Experience with BIIB105 57
3.2.3.1. Nonclinical Experience 57
3.2.3.2. Clinical Experience 60
3.3. Benefit-Risk Assessment 60
4. STUDY OBJECTIVES AND ENDPOINTS 62
5. STUDY DESIGN 66
5.1. Study Overview 66
5.1.1. Part 1 66
5.1.2. Part 2 67
5.2. Study Duration for Participants 67
5.2.1. Study Duration for Participants in Part 1 67
5.2.2. Study Duration for Participants in Part 2 68
5.3. Dosing 69

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5.3.1. Dose Escalation (Part 1) 69
5.3.2. Dosing (Part 2) 70
5.4. Study and Cohort Stopping Rules 71
5.4.1. Cohort Suspension 71
5.4.2. Dose Termination 72
5.4.3. Study Termination 73
5.5. Unscheduled Visits 73
5.6. End of Study 74
5.6.1. End of Part 1 74
5.6.2. End of Study 74
6. STUDY POPULATION 75
6.1. Inclusion Criteria 75
6.1.1. Part 1 75
6.1.2. Part 2 76
6.2. Exclusion Criteria 77
6.2.1. Part 1 77
6.2.2. Part 2 79
6.3. Screening, Retesting, and Screen Failures 81
6.3.1. Screening 81
6.3.2. Retesting 82
6.3.3. Screen Failures 82
7. STUDY TREATMENT 84
7.1. Regimen 84
7.2. Study Treatment Management 85
7.3. Study Treatment 85
7.3.1. BIIB105 85
7.3.1.1. Preparation 85
7.3.1.2. Storage 85
7.3.1.3. Handling and Disposal 86
7.3.1.4. Accountability 86
7.3.2. Placebo 86
7.4. Blinding Procedures 86

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7.5. Precautions 87
7.6. Compliance 87
7.7. Concomitant Therapy and Procedures 87
7.7.1. Concomitant Therapy 87
7.7.1.1. Allowed Concomitant Therapy 87
7.7.1.2. Disallowed Concomitant Therapy 88
7.7.2. Concomitant Procedures 88
7.8. Continuation of Treatment 89
8. RULES FOR DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL FROM STUDY FOR INDIVIDUAL PARTICPANTS 90
8.1. Discontinuation of Study Treatment 90
8.2. Lost to Follow-Up 90
8.3. Withdrawal of Participants From the Study 91
9. SAFETY ASSESSMENTS 92
9.1. Clinical Assessments 92
9.2. Laboratory Assessments 92
9.3. Product-Specific Safety Assessments 93
10. PHARMACOKINETIC ASSESSMENTS 94
11. PHARMACODYNAMIC AND EFFICACY ASSESSMENTS 95
11.1. Pharmacodynamic Assessments 95
11.2. Assessments of Clinical Function and Survival 95
11.2.1. Slow Vital Capacity 95
11.2.2. ALS Functional Rating Scale-Revised (standard) 96
[redacted] 96
[redacted] 96
[redacted] 96
11.2.6. Handheld Dynamometry 97
[redacted] 97
[redacted] 97
[redacted] 97
11.2.10. Participant Ventilation Diary 97
11.2.11. Collection of Vital Status Before and After Study Withdrawal or Completion 98

11.3. Pharmacogenetic and Genetic Assessments 98
[redacted] [redacted] 99
12. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES 100
12.1. Definitions 100
12.1.1. Adverse Event 100
12.1.2. Serious Adverse Event 100
12.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments 101
12.2. Safety Classifications 101
12.2.1. Investigator Assessment of Events 101
12.2.2. Relationship of Events to Study Treatment or Lumbar Puncture 102
12.2.3. Severity of Events 103
12.2.4. Expectedness of Events 103
12.3. Monitoring and Recording Events 103
12.3.1. Adverse Events 103
12.3.2. Serious Adverse Events 103
12.3.3. Immediate Reporting of Serious Adverse Events 104
12.3.3.1. Deaths 104
12.3.4. Suspected Unexpected Serious Adverse Reactions 104
12.4. Procedures for Handling Special Situations 105
12.4.1. Pregnancy 105
12.4.2. Overdose 105
12.4.3. Medical Emergency 105
12.4.3.1. Unblinding for Medical Emergency 106
12.5. Contraception Requirements 106
12.6. Safety Responsibilities 107
12.6.1. The Investigator 107
12.6.2. The Sponsor 108
13. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE 109
13.1. General Considerations 109
13.2. Analysis Populations 109
13.2.1. Part 1 109

13.2.2. Part 2 109
13.2.3. Integrated Part 1 and Part 2 110
13.3. Methods of Analysis 110
13.3.1. Safety 110
13.3.1.1. Adverse Events 110
13.3.1.2. Laboratory Results 111
13.3.1.3. Vital Signs 111
13.3.1.4. C-SSRS 111
13.3.1.5. Electrocardiogram 111
13.3.2. Pharmacokinetics 111
13.3.3. Pharmacodynamics/Biomarkers 112
13.3.4. Clinical Function and Quality of Life Measures 112
13.3.5. Time to Death or Permanent Ventilation, Time to Death 113
[redacted] 113
13.4. Interim Analyses 113
13.5. Sample Size Considerations 114
14. ETHICAL REQUIREMENTS 115
14.1. Declaration of Helsinki 115
14.2. Ethics Committee 115
14.3. Changes to Final Protocol 116
14.4. Informed Consent 116
14.5. Participant Data Protection 117
14.6. Compensation for Injury 117
14.7. Conflict of Interest 117
14.8. Study Report Signatory 117
14.9. Registration of Study and Disclosure of Study Results 117
14.10. Retention of Study Data 118
15. KEY ROLES AND STUDY GOVERNANCE COMMITTEES 119
15.1. Vendors 119
15.1.1. Contract Research Organization 119
15.1.2. Interactive Response Technology 119
15.1.3. Electronic Data Capture 119

15.1.4. Digital Clinical Outcomes Data Capture 119
15.1.5. Central Laboratories for Laboratory Assessments 119
15.1.6. Central Facility for Other Assessments 120
15.2. Study Committees....120
15.2.1. Safety Surveillance Team 120
16. ADMINISTRATIVE PROCEDURES 121
16.1. Study Site Initiation 121
16.2. Quality Control and Quality Assurance....121
16.3. Monitoring of the Study....121
16.4. Study Funding....122
16.5. Publications....122
16.6. Public Health Emergencies....122
17. REFERENCES 124
18. SIGNED AGREEMENT OF THE STUDY PROTOCOL....127

LIST OF TABLES

Table 1: Part 1 Schedule of Activities: Cohorts A, B, C1, C2....27
Table 2: Part 1 Schedule of Activities: Cohort D1 and D2....32
Table 3: Schedule of Activities Part 2 (all Cohorts) 41
Table 4: Predicted *ATXN2* mRNA Reduction (Cortex and Spinal Cord), ATXN2 protein reduction (CSF), and Safety Margins at Steady-state at Proposed Dose Levels 55

LIST OF FIGURES

Figure 1: Study Design....26

1. KEY STUDY ELEMENTS

1.1. Synopsis

Protocol Title:	A Phase 1/2 Multiple-Ascending-Dose Study With a Long-Term Open-Label Extension to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Effect on Disease Progression of BIIB105 Administered Intrathecally to Adults With Amyotrophic Lateral Sclerosis With or Without PolyCAG Expansion in the *ATXN2* Gene
Protocol Number:	275AS101
Version Number:	5
Name of Study Treatment:	Research Name: BIIB105 Generic Name: Not Applicable
Study Phase:	1/2
Study Indication:	Amyotrophic lateral sclerosis (ALS) and ALS associated with ataxin-2 (*ATXN2*) polyCAG expansion (polyQ-ALS)
Study Rationale:	ALS is a rare neurodegenerative disease resulting in pathologic loss of motor neurons and their axons within the cortex, brainstem, spinal cord, and peripheral nerves with functional decline and death, typically from respiratory failure. There are no effective drug therapies to cure or substantially moderate functional decline or improve survival. A hallmark of ALS pathogenesis in the majority of patients is the presence of cytoplasmic inclusions containing aggregated TDP-43 in motor neurons [Ling 2013; Neumann 2006]. TDP-43 is a ubiquitously expressed protein that plays a variety of roles in RNA processing. Mutations in the *TDP-43* gene have been shown to cause familial ALS; however, most patients do not carry an associated *TDP-43* genetic mutation, suggesting that abnormal cytoplasmic aggregation of the wild-type protein may play a role in disease pathogenesis [Scotter 2015a, 2015b]. A potential therapeutic approach to indirectly affect TDP-43 is modulation of the ATXN2 protein. While the exact mechanism remains unclear, ATXN2 modulation has been shown to impact TDP-43 toxicity in nonclinical models, where toxicity caused by overexpression of TDP-43 was enhanced with increased

expression of ATXN2 and was reduced when ATXN2 levels were depleted [Becker 2017; Elden 2010].

These nonclinical findings linking ATXN2 to ALS have been supported by human genetic studies and pathological observations in ALS patient tissue. Intermediate-length expansion of the polyCAG region in *ATXN2* has been identified as a significant risk factor for developing ALS [Elden 2010; Neuenschwander 2014; Sproviero 2017]. This repeat region encodes a polyQ segment at the N-terminus of the ATXN2 protein, and when expanded, is believed to stabilize the protein [Elden 2010]. Additionally, retrospective analysis of patients with ALS harboring a polyCAG expanded allele (polyQ patients) compared with matched patients with ALS harboring only normal polyCAG length alleles has shown that patients with ATXN2 polyQ demonstrate faster clinical progression, as measured by the ALSFRS-R and respiratory vital capacity, suggesting that ATXN2 polyQ expansions also confer a risk of more aggressive disease [McMillan 2020]. Finally, ATXN2 protein lacking a polyQ expansion has been found to be aberrantly localized in ~25% of motor neurons in multiple ALS patients [Elden 2010].

BIIB105 is a novel ASO being developed for the treatment of ALS. The ASO targets the *ATXN2*-mRNA for degradation, as a means to decrease ATXN2 protein levels and thereby mitigate TDP-43 toxicity as seen in nonclinical models.

Given the rapidly progressing, life-threatening, and rare nature of the disease as well as the high unmet medical need in ALS, the first-in-human Phase 1/2 study will be a two-part evaluation of BIIB105 in adult participants with ALS and polyQ-ALS. Part 1 will be a placebo-controlled MAD assessment of the safety, tolerability, pharmacokinetics, pharmacodynamics, and effect on disease progression of BIIB105. Part 2 will be an extension study to assess the long-term safety, tolerability, pharmacokinetics, pharmacodynamics, and effect on disease progression of BIIB105 in participants who complete Part 1 through Week 25 (Day 175 Visit for Cohorts A, B, C1, and C2; Day 176 Visit for Cohorts D1 and D2).

This study design will minimize the number of participants receiving subtherapeutic doses and/or dosing durations. For all cohorts in Part 1, the 72-hour safety data review following sentinel dosing of the first 2 participants of each dosing cohort and the 7-day safety review for each participant after administration of the first dose and prior to administration of the

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	second dose will allow evaluation of potential acute safety and tolerability findings in each participant prior to the administration of additional doses, similar to a single-ascending-dose study design. Part 2 will provide up to 104 weeks of dosing of BIIB105 for study participants who complete 25 weeks in Part 1. The safety, PK, PD, and clinical function data collected from Part 2 will allow for the understanding of the long-term effect of BIIB105 in participants with ALS and polyQ-ALS.
Rationale for Starting Dose and Maximum Exposure:	A single-dose, NHP, toxicity study identified a maximum tolerated dose ([redacted] mg) and reversible AEs at [redacted] mg, which can be monitored clinically. The maximum dose of [redacted] mg used in this study, will provide an approximately [redacted]-fold safety margin to the HED ([redacted] mg) of the NOAEL of [redacted] mg in the 13-week NHP repeat-dose toxicology study and a [redacted]-fold safety margin of the HED ([redacted]) of the NOAEL of [redacted] mg in the 41-week NHP repeat-dose study. The selection of the starting dose for this study is based on the NOAEL dose of [redacted] mg, established in the 13-week toxicology study in NHPs, and on the expected PD of BIIB105 in the brain cortex and spinal cord. The monkey provided the lowest HED, which was calculated to be [redacted] mg utilizing a CSF volumetric scaling factor of 10. This represents a conservative estimate of CSF volume ratio between humans and monkeys. The HED value was divided by the conventional safety factor of 10 to yield the MRSD, [redacted] mg. The proposed [redacted] mg starting dose is below the MRSD, has a [redacted]-fold safety factor over the HED ([redacted] mg) of the NOAEL from the 13-week toxicology study, and is expected to produce minimal to moderate pharmacologic effects in the brain and spinal cord, respectively. The preclinical evidence suggests a dose-dependent relationship between ATXN2 levels and clinical outcomes in TDP-43 models of disease [Becker 2017; Elden 2010]. In TDP-43 transgenic mice, ASO-induced reduction of *Atxn2* mRNA levels in CNS tissues by 77% on average resulted in a 35% increase in median lifespan compared with control ASO littermates [Becker 2017]. An mRNA reduction of approximately [redacted]% is therefore considered the target BIIB105 PD effect in humans that could be indicative of potential clinical efficacy. The MRSD of [redacted] mg is estimated to reduce *ATXN2* mRNA levels approximately [redacted]% in the cortex and approximately [redacted]% in the spinal cord, after [redacted] doses. In consideration of the higher reduction of *ATXN2* mRNA in spinal cord, a starting dose of [redacted] mg is anticipated to reduce *ATXN2* mRNA levels by approximately [redacted]% in the cortex and

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[redacted]% in the spinal cord. A maximum dose of [redacted] mg is proposed at this time and is estimated to reduce *ATXN2* mRNA levels in the cortex by approximately [redacted]% and in the spinal cord by approximately [redacted]%, at steady state, with a safety margin of [redacted]-fold under the NOAEL in the 13-week NHP study and a safety margin of [redacted]-fold under the NOAEL of [redacted] mg in the 41-week NHP study. Postmortem tissue analyses from both the 13- and 41-week toxicology studies in NHP showed that the CNS tissue ATXN2 protein levels are reflective of CNS tissue *ATXN2* mRNA levels. [redacted]

The doses in this study may be adjusted as the study progresses, based on results from the comparison of the human safety, PK, and/or PD data (including CSF ATXN2 protein levels) from the lower cohorts and the PK/PD effects predicted by the model. However, the top dose will not exceed [redacted] mg and dose escalations will not exceed 2× when above MRSD.

In Part 1 and Part 2, the length of the dosing interval during the 28-day loading period (3 doses administered once every 2 weeks) is designed to yield a rapid onset of steady-state exposure by the third dose on Day 29. Following the loading period, dosing every 4 weeks is projected to maintain steady-state exposure based on the whole-body physiologically based PK model.

Study Objectives and Endpoints:

Part 1

Primary Objective	Primary Endpoint
To evaluate the safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.	Incidence of AEs and SAEs in Part 1
Secondary Objectives	**Secondary Endpoints**
To assess the PK profile of BIIB105 in serum and CSF of participants with ALS or polyQ-ALS.	Serum and CSF concentrations of BIIB105 in Part 1. To evaluate the following serum PK parameters in Part 1: • AUC_{inf} • AUC_{last} • C_{max} • T_{max} • $t_{½}$
To evaluate the biomarker effect of BIIB105 in participants with ALS or polyQ-ALS.	Secondary biomarker measure: • Changes from baseline in plasma levels of NfL

Part 2

Primary Objective	Primary Endpoint
To evaluate the long-term safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.	Incidence of AEs and SAEs in Part 2

Integrated Part 1 and 2

Primary Objective	Primary Endpoint
To evaluate the long-term safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.	Incidence of AEs and SAEs during the BIIB105-treated period in Part 1 and/or Part 2
Secondary Objectives	**Secondary Endpoints**
To assess the long-term PK profile of BIIB105 in serum and CSF of participants with ALS or polyQ-ALS.	Serum and CSF concentrations of BIIB105 in Part 1 and Part 2. • CSF trough PK concentration • Serum PK concentration if available
To evaluate the long-term biomarker effect of BIIB105 in participants with ALS or polyQ-ALS, and to assess the impact of earlier initiation of BIIB105 (i.e., at start of Part 1) compared with delayed initiation of BIIB105 (i.e., at start of Part 2) on biomarkers.	Secondary biomarker measure: • Changes from Part 1 baseline in plasma levels of NfL
To evaluate the long-term effect of BIIB105 on measures of clinical function and to assess the impact of earlier initiation of BIIB105 (i.e., at start of Part 1) compared with delayed initiation of BIIB105 (i.e., at start of Part 2) on measures of clinical function.	Changes from Part 1 baseline in the following assessments: • SVC • ALSFRS-R score • Muscle strength, as measured by HHD Survival analyses: • Time to death or permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days) • Time to death

- Time to death, incorporating post-study withdrawal or study completion vital status data

[redacted]

Study Design:	Part 1 is a Phase 1/2, randomized, double-blind, placebo-controlled, MAD evaluation of the safety, tolerability, PK, PD, and effect on disease progression of BIIB105, administered IT to approximately 98 participants (76 participants with ALS and 22 participants with polyQ-ALS) at approximately 15 sites globally. Cohorts A, B, C1, and C2 will receive up to 5 doses over approximately 3 months. Cohorts D1 and D2 will receive up to 8 doses over approximately 6 months. Part 2 is an extension study to assess the long-term safety, tolerability, pharmacokinetics, pharmacodynamics, and effect on disease progression of BIIB105 administered to adults with ALS and polyQ-ALS who complete Part 1 through Week 25.
Study Location:	Approximately 15 sites globally are planned for this study.
Study Population:	This study will be conducted in participants who meet the following criteria. Criteria for inclusion of participants Part 1: Aged at least 18 years at the time of informed consent or participant meets the minimum age of consent in accordance with national regulations (whichever is higher). Participants in Cohorts A, B, C1 and D1, must meet the laboratory-supported probable, probable, or definite criteria for diagnosing ALS according to the World Federation of Neurology El Escorial criteria (revised according to the Airlie House Conference 1998 [Brooks 2000]). Participants in Cohort C2 and D2, must meet any of the prior conditions, but may also only meet clinically possible criteria for diagnosing ALS, or exhibit weakness attributable to ALS in the presence of ATXN2 intermediate repeats. In participants in Cohorts C2 and D2, confirmed intermediate CAG/CAA repeat expansion in the *ATXN2* gene as defined by at least 1 allele carrying 30 to 33 CAG/CAA repeats. SVC criteria:

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	In participants in Cohorts A, B, C1, and D1, SVC ≥ 60% of predicted value as adjusted for sex, age, and height (from the sitting position). In participants in Cohorts C2 and D2, SVC ≥ 50% of predicted value as adjusted for sex, age, and height (from the sitting position). Criteria for exclusion of participants from Part 1: In participants in Cohorts A, B, and C1, prescreening ALSFRS-R slope > -***0.4*** points/month, where prescreening ALSFRS-R slope is defined as: (ALSFRS-R score at Screening - 48) / (months from date of symptom onset to date of Screening). Part 2 will be conducted in participants with ALS or polyQ-ALS who have completed Part 1 through Week 25 (Day 175 Visit for Cohorts A, B, C1, C2; Day 176 Visit for Cohorts D1 and D2). Detailed criteria are described in Section 6.
Number of Planned Participants:	A total of approximately 98 participants are planned to be randomized in the study. Participants who withdraw may be replaced in a cohort at the discretion of the Sponsor. With potential replacement, approximately 108 participants could be randomized in this study.

Treatment Groups:

In Part 1:

Participants with ALS:

Cohort A: BIIB105 5 mg (6 participants) or placebo (2 participants)

Cohort B: BIIB105 20 mg (6 participants) or placebo (2 participants)

Cohort C1: BIIB105 60 mg (9 participants) or placebo (3 participants)

Cohort D1: BIIB105 120 mg (approximately 36 participants) or placebo (approximately 12 participants)

Participants with polyQ-ALS:

Cohort C2: BIIB105 60 mg (3 participants) or placebo (1 participant)

Cohort D2: BIIB105 120 mg (approximately 12 participants) or placebo (approximately 6 participants)

Participants in Cohorts A, B, C1, and C2 will receive 3 loading doses administered every 2 weeks (on Days 1, 15, and 29), followed by 2 maintenance doses administered once every 4 weeks (on Days 57 and 85), for a total of 5 doses over approximately 13 weeks.

Participants in Cohorts D1 and D2 will receive 3 loading doses administered every 2 weeks (on Days 1, 15, and 29), followed by 5 maintenance doses administered once every 4 weeks (on Days 57, 85, 113, 141, and 169), for a total of 8 doses over approximately 25 weeks.

In Part 2:

Part 2 is an open-label evaluation of BIIB105 administered IT to participants with ALS and polyQ-ALS who have completed Part 1 through Week 25 (Day 175 Visit for Cohorts A, B, C1, C2; Day 176 Visit for Cohorts D1, D2). Participants will receive up to approximately 41 doses in Part 2. Two dose levels will be administered – participants from Part 1 Cohorts A, B, C1, and C2 will receive 60 mg BIIB105; participants from Part 1 Cohorts D1 and D2 will receive 120 mg BIIB105.

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	In Part 2, the 60 mg dose may be increased, based on Sponsor review of emerging safety, PK, PD, and/or clinical data from the study, to doses up to 120 mg. Doses in Part 2 may also be decreased, based on Sponsor review of emerging safety, PK, PD, and/or clinical data from the study.
Sample Size Determination:	Part 1: The sample size of this first-in-human clinical study was selected with the goal of balancing between safety and tolerability considerations in dose escalation and obtaining sufficient initial information related to the safety and biological activities of BIIB105. Sample sizes of 6 participants receiving active treatment in lower dose Cohorts A and B will allow an [redacted]% or greater probability to observe at least 1 occurrence of an AE with event rates of [redacted]% or greater. The sample size of 9, 36, and 12 participants exposed to active doses in Cohorts C1, D1, and D2, respectively, allow an [redacted]% or greater probability to observe at least 1 occurrence of an AE with event rates of [redacted]%, [redacted]%, and [redacted]%, or greater, respectively. Cohort C2 will expose 3 participants with polyQ-ALS to active treatment as part of additional dose escalation step specifically for participants with intermediate-repeat CAG expansions in *ATXN2* gene as they may be more sensitive to the effects of BIIB105. The sample size of 3 was selected solely as precaution step before exposing participants with polyQ-ALS to 120 mg dose of BIIB105 in Cohort D2. The sample size of Cohort D1 provides approximately [redacted]% power to detect a [redacted]% difference in the ratio to baseline in plasma NfL, in the BIIB105 versus placebo group, based on Cohort D1 120 mg data (N on BIIB105 = 36) vs pooled placebo data across Cohorts A through D1 (N = 19), with 2-sided [redacted]% significance level, assuming [redacted]% SD in both groups. Part 2: The sample size of this extension is based on the sample size of Study 275AS101 Part 1. Up to approximately 98 participants will be dosed in Study 275AS101 Part 2.
Statistical Methods:	Placebo data in Part 1 may be pooled across cohorts for analyses. The Pooled Placebo 1 population is defined as participants from

Cohorts A, B, C1, and D1 who received placebo in Part 1. The Pooled Placebo 2 population is defined as participants from Cohorts C2 and D2 who received placebo in Part 1.

Safety and tolerability: For analyses of Part 1, safety data will be summarized by dose level and treatment assignment in Part 1 (BIIB105 5 mg [Cohort A], 20 mg [Cohort B], 60 mg [Cohorts C1+ C2], 120 mg [Cohorts D1+D2], Pooled Placebo 1+2), as well as by cohort and treatment assignment in Part 1 (BIIB105-treated Cohorts A, B, C1, C2, D1, and D2; Pooled Placebo 1 and Pooled Placebo 2). For analyses of Part 2, safety data will be summarized by dose level in Part 2 (BIIB105 60 mg vs BIIB105 120 mg). [redacted] For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, safety data from the BIIB105-treated periods in Part 1 and Part 2 will be summarized, with baseline defined as the first dose of 120 mg BIIB105, regardless of whether the participant started this dose in Part 1 or Part 2. [redacted] To assess the overall safety profile of 60 mg BIIB105, integrated Part 1 and 2 safety data may be presented for any participant who received at least one dose of 60 mg BIIB105, with baseline defined as first dose of 60 mg BIIB105. To assess the overall safety profile of 120mg BIIB105, integrated Part 1 and 2 safety data may be presented for any participant who received at least one dose of 120 mg BIIB105, with baseline defined as the first dose of 120 mg BIIB105. The incidence of treatment-emergent AEs, SAEs, deaths, and AEs leading to treatment discontinuation, at minimum, will be summarized by system organ class and preferred term. Laboratory data will also be summarized. Summary statistics for actual values and changes from baseline will be presented for quantitative laboratory data. In addition, shift tables will be used to tabulate the shifts from baseline to high/low status for each laboratory test. Incidence of clinically relevant abnormalities/changes from baseline in vital signs and ECGs will also be summarized. C-SSRS data will also be summarized using frequency tables.

PK: Serum and CSF BIIB105 concentrations will be summarized using descriptive statistics and, where warranted, plotted graphically over time both on a linear and logarithmic scale. For analyses of Part 1, PK data will be summarized by dose level in Part 1 (BIIB105-treated 5 mg [Cohort A], 20 mg [Cohort B], 60 mg [Cohorts C1 + C2], and 120 mg [Cohorts D1 + D2]). For

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integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, PK data from the BIIB105-treated periods in Part 1 and Part 2 will be summarized, with baseline defined as the first dose of 120 mg BIIB105, regardless of whether the participant started this dose in Part 1 or Part 2. [redacted] To assess the overall PK profile of 60 mg BIIB105, integrated Part 1 and 2 PK data may be presented for any participant who received at least one dose of 60 mg BIIB105, with baseline defined as first dose of 60 mg BIIB105. To assess the overall PK profile of 120mg BIIB105, integrated Part 1 and 2 PK data may be presented for any participant who received at least one dose of 120 mg BIIB105, with baseline defined as the first dose of 120 mg BIIB105.

[redacted]

Clinical Function and Quality of Life Measures:

The actual scores and changes from baseline in each clinical function and quality of life measure will be summarized by visit and dose level using descriptive statistics. In addition, each clinical function quality of life measure may be analyzed using an ANCOVA model.

[redacted]

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, treatment groups will be defined as Early-start (i.e., those who initiated BIIB105 in Part 1) and Placebo/Delayed-start (i.e., those who received placebo in Part 1), with baseline defined as Part 1 baseline. Clinical function data will be presented by the 120 mg dose level and treatment group (Cohort D1+D2 Early-start vs Placebo/Delayed-start). They will also be presented by Cohort and treatment group as a sensitivity analysis (Cohort D1

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Early-start vs Placebo/Delayed-start; Cohort D2 Early-start vs Placebo/Delayed-start).

Survival analyses: Time to death and time to death or permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days) will be summarized using Kaplan-Meier curves based on the starting time of randomization into Study 275AS101 Part 1, and time of symptom onset. Post-withdrawal or study completion vital status data will also be incorporated into a separate analysis of time to death.

Interim Analysis: One or more interim analyses of unblinded key safety, secondary, [redacted] endpoints (including PK, PD, clinical function) may be conducted following the completion of dosing of 1 or more dose cohorts in Part 1 to allow for the confirmation of dose escalation decisions and/or to inform decisions on the BIIB105 clinical development program. If, based on an interim analysis Part 1, the Study Sponsor decides to terminate Part 1 of the study without terminating Part 2, participants who are active in Part 1 at the time of the Sponsor's decision will have the opportunity to end Part 1 and screen and enroll into Part 2. In this scenario, participants screening for Part 2 will not have to meet Section 6.1.2 Part 2 Inclusion Criterion #2 (having completed Part 1 through Week 25) to be eligible for Part 2. Additional interim analyses may be performed during the conduct of Part 2 using data from Part 2 alone and/or integrated data from Part 1 and Part 2. Specifics will be detailed in the statistical analysis plan. The participants, site staff, and Sponsor study team responsible for site monitoring and data management will remain blinded to treatment assignment during the ongoing data review, as well as during interim analyses, to minimize the potential for bias. Details will be provided in the Unblinding Plan and specific interim analysis plans.

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Visit Schedule:	Part 1: Participants in Cohorts A, B, C1, and C2 will have up to 13 CVs and 9 TCs during the study, which include at least 1 Screening Visit, 5 Dosing Visits of which the first dose will require an inpatient stay of 2 days, 7 Follow-up Visits, and 9 TCs. Visit days are calculated with respect to Day 1 (the date of first dose). Participants in Cohorts D1 and D2 will have up to 19 CVs and 15 TCs which will include at least 1 Screening Visit, 8 Dosing Visits of which the first will require an inpatient stay of 2 days, up to 10 Follow-up Visits, and up to 15 TCs. Participants in Cohorts D1 and D2 who enroll in Part 2 will not complete the Follow-up Visits and TCs in Part 1 that occur after enrollment in Part 2. Part 2: Participants will have up to approximately 44 CVs and 43 TCs during Part 2 of the study, which will include at least 1 Screening Visit, up to approximately 41 Dosing Visits, 2 Follow-Up Visits, and up to 43 TCs. For participants from Cohorts D1 and D2, the Screening Visit for Part 2 may be combined with their Part 1 Day 169 and/or Day 176 Visits. Study assessments conducted at each visit are listed in Table 1.
Duration of Study Participation:	Part 1: Study duration for each participant in Cohorts A, B, C1, and C2 will be approximately 29 weeks: 4-week Screening Period 13-week Treatment Period Approximately 12-week Follow-up Period Study duration for each participant in D1and D2 will be between approximately 29 and 41 weeks: 4-week Screening Period

25-week Treatment Period

Approximately 12-week Follow-up Period (only completed if the participant does not enter Part 2 after the Treatment Period)

Part 2:

Study duration for all participants will be up to approximately 172 weeks:

4-week Screening Period (for participants from Cohorts D1 and D2, Screening Period begins with Day 169 Visit of Part 1)

Up to approximately 156-week Treatment Period: either 104 weeks, or until the last participant enrolled has had the opportunity for their Part 2 Day 365 visit (Week 52), whichever occurs later.

Approximately 12-week Follow-up Period

Benefit-Risk Analysis:

The potential benefit of BIIB105 in ALS has not been established. The study has been designed with appropriate dose escalation, safety monitoring, and stopping rules to minimize risks to participants. The results of this study may offer key insights into the development of a disease-modifying therapy for ALS.

This is a first in human study, thus the risk in humans is unknown. Emerging clinical data can be found in the Investigator's Brochure.

Nonclinical work with *Atxn2* homozygous knockout mice suggests that ATXN2 reduction could be associated with risks of metabolic complications (adult-onset obesity and insulin resistance) and subtle neurological deficits such as motor hyperactivity and abnormal fear conditioning [Huynh 2009; Kiehl 2006; Lastres-Becker 2008]. Human data from the Genome-Wide Association Studies database suggest that variation in ATXN2 could be associated with changes in blood pressure and cardiometabolic phenotypes [Auburger 2014]. From the nonclinical safety studies in NHPs, the adverse effect level was considered to be [redacted] mg based on severe but reversible and monitorable clinical signs: 1 of 3 animals exhibited increased muscle tone, whole body spasms, and tremors that required

administration of diazepam. The animal fully recovered by [redacted] hours. No adverse metabolic effects were seen in toxicology studies. Participants will be monitored in the clinical setting with neurological and physical examinations and careful monitoring of blood chemistries, among other safety assessments.

Reproductive toxicity studies were conducted in mice and rabbits using SC administration of BIIB105 once every other day. In a definitive combined fertility and embryo-fetal development study in male and female mice, there was no effect of BIIB105 on fertility in either sex. BIIB105 did not produce any fetal external, visceral, or skeletal malformations or variations in mice or rabbits. However, there were BIIB105-related effects on embryo-fetal development in both species. In mice, there were lower mean fetal body weights that were considered adverse at the highest dose tested ([redacted] mg/kg). In a dose-range finding study in rabbits, dose-limiting BIIB105-related findings included body weight losses, reduced food consumption, and abortions. There was very limited fetal exposure in mice only.

Due to these adverse findings in the reproductive toxicity nonclinical studies, all men and women of childbearing potential must use highly effective contraception during the study and for at least [redacted] after the study (for female participants) and at least [redacted] after the study (for male participants).

Although LP is generally considered a safe procedure, certain complications can occur in a subset of patients. These may include, but are not limited to, back pain, headache, nausea, infection, bleeding, radicular pain and numbness, and bruising or injury at the injection site. These potential risks can be mitigated by using atraumatic needles, avoiding contraindicated medications, and testing coagulation and platelet counts prior to the procedure. Importantly, life-threatening cerebral herniation is a possible complication of a LP procedure.

ALS is a debilitating, rapidly progressing, and life-threatening disease with a high unmet need for effective therapies. Overall, the benefit-risk profile is positive for the development of BIIB105 for the treatment of ALS and polyQ-ALS.

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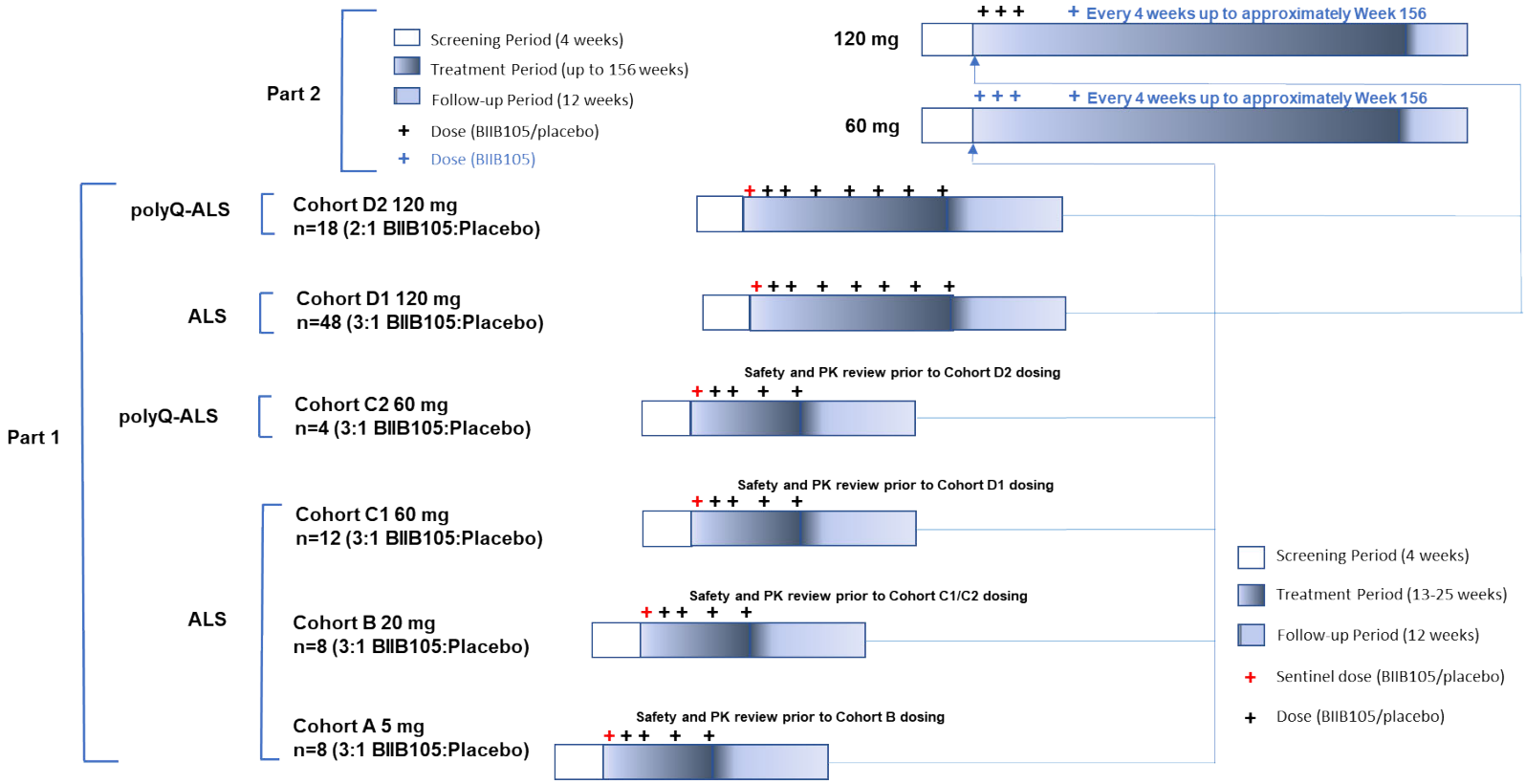
Study Design Schematic

Figure 1: Study Design



Schedule of Activities

Table 1: Part 1 Schedule of Activities: Cohorts A, B, C1, C2

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Dose 4	TC	CV	TC	Dose 5	TC	CV	TC	Follow-Up Period			TC	UV
Days		1		2	8 (±2)	15 (±3)	16 (+1)	22 (±3)	29 (±3)	30 (+1)	36 (±3)	50 (±3)	57 (±3)	58 (+1)	64 (±3)	78 (±3)	85 (±3)	86 (+1)	92 (±3)	93 (+1)	130 (±3)	131 (+1)	175 (±3)	176 (+1)	
Assessments	-28 to -1	Predose	Dosing/ Postdose	(24 ±1 h) postdose																					
ICF (Main)	X																								
ICF (Informant/ Caregiver)[2]	X																								
Eligibility Criteria	X																								
Demographics	X																								
Medical History	X	X																							
Confirmation of ALS Diagnosis	X																								
Blood Sample for DNA (assessment of polyQ status and ALS-causative genes)	X																								
Clinical Laboratory Samples for Viral Serology[3]	X																								

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Dose 4	TC	CV	TC	Dose 5	TC	CV	TC	Follow-Up Period			TC	UV
																					CV	TC	Final/ ET Visit		
Days		1		2	8 (±2)	15 (±3)	16 (+1)	22 (±3)	29 (±3)	30 (+1)	36 (±3)	50 (±3)	57 (±3)	58 (+1)	64 (±3)	78 (±3)	85 (±3)	86 (+1)	92 (±3)	93 (+1)	130 (±3)	131 (+1)	175 (±3)	176 (+1)	
Assessments	-28 to -1	Predose	Dosing/ Postdose	(24 ±1 h) postdose																					
Serum Pregnancy Test[4]	X																								
Urine Pregnancy Test[5]		X				X			X				X				X						X		
FSH Test[6]	X																								
Physical Examination[7]	X	X		X	X	X		X	X		X		X		X		X		X		X		X		X
Neurological Examination (cranial nerves, cerebellar function, motor, and reflexes)[8]	X	X	X	X	X	X		X	X		X		X		X		X		X		X		X		X
MMSE		X			X				X				X				X								
Weight	X	X																	X				X		
Height	X																								
12-Lead ECG[9]	X	X	X	X		X		X	X		X		X		X		X		X				X		X
Vital Signs (temperature, blood pressure, heart rate, respiratory rate)[9]	X	X	X	X	X	X		X	X		X		X		X		X		X		X		X		X
SVC[10]	X	X				X			X				X				X				X		X		

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Dose 4	TC	CV	TC	Dose 5	TC	CV	TC	Follow-Up Period			TC	UV
Days		**1**		**2**	**8 (±2)**	**15 (±3)**	**16 (+1)**	**22 (±3)**	**29 (±3)**	**30 (+1)**	**36 (±3)**	**50 (±3)**	**57 (±3)**	**58 (+1)**	**64 (±3)**	**78 (±3)**	**85 (±3)**	**86 (+1)**	**92 (±3)**	**93 (+1)**	**130 (±3)**	**131 (+1)**	**175 (±3)**	**176 (+1)**	
Assessments	**-28 to -1**	**Predose**	**Dosing/ Postdose**	**(24 ±1 h) postdose**																	**CV**	**TC**	**Final/ ET Visit**		
ALSFRS-R[11]	X	X							X		X		X		X		X		X		X		X		
[redacted]																									
Randomization/ Admission to Inpatient Facility		X																							
Study Treatment Administration[12]			X			X			X				X				X								
C-SSRS Questionnaire[13]		X			X	X		X	X		X		X		X		X		X		X		X		X
Clinical Laboratory Samples for Hematology, Coagulation, Blood Chemistry, and Urinalysis[14]	X	X		X		X			X				X		X		X		X		X		X		

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Dose 4	TC	CV	TC	Dose 5	TC	CV	TC	Follow-Up Period			TC	UV
Days		1		2	8 (±2)	15 (±3)	16 (+1)	22 (±3)	29 (±3)	30 (+1)	36 (±3)	50 (±3)	57 (±3)	58 (+1)	64 (±3)	78 (±3)	85 (±3)	86 (+1)	92 (±3)	93 (+1)	130 (±3)	131 (+1)	175 (±3)	176 (+1)	
Assessments	-28 to -1	Predose	Dosing/ Postdose	(24 ±1 h) postdose																					
Serum Sampling for PK[15]		X	X	X	X	X			X				X				X		X						
Blood Sampling for Biomarkers[10]		X							X				X				X				X		X		
[redacted]																									
CSF Sampling[16]		X				X			X				X				X		X		X		X		
Discharge From Inpatient Facility				X																					
Concomitant Therapy and Procedures Recording		----------Ongoing----------																							X
AE Recording		----------Ongoing----------																							X
SAE Reporting		----------Ongoing----------																							X

[1] Screening assessments can be performed on multiple days (up to 7 days) for ease of participant burden.
[2] An informant/caregiver should be available at Screening, and the participation of the same informant/caregiver for the duration of the study. The informant/caregiver must provide written informed consent to participate in the study prior to providing any information on either themselves and/or participants.
[3] Including blood samples for HIV, HCV, and hepatitis B virus.
[4] For women of childbearing potential only; to be performed centrally.
[5] Performed predose on dosing days for women of childbearing potential only; to be performed locally

[6] To be conducted only in female participants presenting with a history of being postmenopausal to confirm postmenopausal status.
[7] Limited physical examination from Day 8 to Day 175 and UV per the Investigator's discretion.
[8] On dosing days, to be assessed predose and at 3 and 6 hours postdose. At UV, a limited neurological examination may be performed per the Investigator's discretion.
[9] On dosing days, ECG and vital signs are to be assessed just prior to drawing PK blood samples at predose, and 2 and 4 hours postdose. Vital signs may be measured in either the sitting or supine position, and ECGs are to be done in triplicate after resting in the supine position for ≥ 5 minutes. During UV, ECGs are to be done if medically indicated. All ECGs will be read by the Investigator at collection and then sent to a central ECG reader for further evaluation and to confirm eligibility at Screening.
[10] On dosing days, to be performed before dosing.
[11] To be collected prior to other assessments and before dosing, on dosing days.
[12] Administered by LP.
[13] Use "Since Last Visit" version of C-SSRS from Day 8 onward. Done predose on dosing days. At UV, may be assessed per the Investigator's discretion.
[14] HbA1c and lipid panel to be assessed at Screening and on Days 1, 85, and 175 only.
[15] To be collected predose and at 1, 2, 4, and 6 hours postdose on dosing days.
[16] To be collected predose on dosing days. Collected by LP. Participants to be observed in the clinic for ~6 hours after the LP procedure on dosing days and for ~1 hour on nondosing days.

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Table 2: Part 1 Schedule of Activities: Cohort D1 and D2

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Doses 4, 5, 6, 7	TC	CV	TC	Dose 8	TC	CV	TC	FU Period[2]				UV
																					CV	TC	Final/ ET Visit	TC	
Days		1		2	8 (±2)	15 (±3)	16 (+1)[4]	22 (±3)	29 (±3)	30 (+1)[4]	36 (±3)	50 (±3)	57, 85, 113, 141 (±3)	58, 86, 114, 142 (+1)[4]	64, 92, 120, 148 (±3)	78, 106, 134, 162 (±3)	169 (±3)[3]	170 (+1)[4]	176 (±3)	177 (+1)[4]	214 (±3)	215 (+1)[4]	259 (±3)	260 (+1)[4]	
Assessments[5]	-28 to -1	Predose	Dosing/Postdose	(24 ±1 h) postdose																					
ICF (Main)	X																								
ICF (Informant/ Caregiver)[6]	X																								
[redacted]																									
Eligibility Criteria	X																								
Demographics	X																								
Medical History	X	X																							
Confirmation of ALS Diagnosis	X																								
Blood Sample for DNA (assessment of polyQ status and ALS-causative genes)	X																								

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Doses 4, 5, 6, 7	TC	CV	TC	Dose 8	TC	CV	TC	FU Period[2]				UV
																						CV	TC	Final/ ET Visit	TC	
Days		1		2	8 (±2)	15 (±3)	16 (+1)[4]	22 (±3)	29 (±3)	30 (+1)[4]	36 (±3)	50 (±3)	57, 85, 113, 141 (±3)	58, 86, 114, 142 (+1)[4]	64, 92, 120, 148 (±3)	78, 106, 134, 162 (±3)	169 (±3)[3]	170 (+1)[4]	176 (±3)	177 (+1)[4]	214 (±3)	215 (+1)[4]	259 (±3)	260 (+1)[4]	
Assessments[5]	-28 to -1	Predose	Dosing/Postdose	(24 ±1 h) postdose																					
Clinical Laboratory Samples for Viral Serology[7]	X																								
Serum Pregnancy Test[8]	X																								
Urine Pregnancy Test[9]		X				X			X				X				X		X		X		X		
FSH Test[10]	X																								
Physical Examination[11]	X	X		X	X	X		X	X		X		X		X		X		X		X		X		X
Neurological Examination (cranial nerves, cerebellar function, motor, and reflexes)[12]	X	X	X	X	X	X		X	X		X		X		X		X		X		X		X		X
MMSE		X			X				X				X				X								
Weight	X	X													X[13]				X				X		

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Doses 4, 5, 6, 7	TC	CV	TC	Dose 8	TC	CV	TC	FU Period[2]				
																							Final/ ET Visit		UV
Days / **Assessments[5]**	-28 to -1	1		2	8 (±2)	15 (±3)	16 (+1)[4]	22 (±3)	29 (±3)	30 (+1)[4]	36 (±3)	50 (±3)	57, 85, 113, 141 (±3)	58, 86, 114, 142 (+1)[4]	64, 92, 120, 148 (±3)	78, 106, 134, 162 (±3)	169 (±3)[3]	170 (+1)[4]	176 (±3)	177 (+1)[4]	214 (±3)	215 (+1)[4]	259 (±3)	260 (+1)[4]	
		Predose	Dosing/Postdose	(24 ±1 h) postdose																					
Height	X																								
12-Lead ECG[14, 15]	X	X	X	X	X	X		X	X		X		X		X		X		X		X		X		X
Vital Signs (temperature, blood pressure, heart rate, respiratory rate)[14]	X	X	X	X	X	X		X	X		X		X		X		X		X		X		X		X
Set Up Study Mobile Device[16]		X																							

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Doses 4, 5, 6, 7	TC	CV	TC	Dose 8	TC	CV	TC	FU Period[2]				
																							Final/ ET Visit		
Days		1		2	8 (±2)	15 (±3)	16 (+1)[4]	22 (±3)	29 (±3)	30 (+1)[4]	36 (±3)	50 (±3)	57, 85, 113, 141 (±3)	58, 86, 114, 142 (+1)[4]	64, 92, 120, 148 (±3)	78, 106, 134, 162 (±3)	169 (±3)[3]	170 (+1)[4]	176 (±3)	177 (+1)[4]	214 (±3)	215 (+1)[4]	259 (±3)	260 (+1)[4]	UV
Assessments[5]	**-28 to -1**	**Predose**	**Dosing/Postdose**	**(24 ±1 h) postdose**																					
[redacted]																									
Participant ventilation diary[19]		X																							
Review ventilation use[20]		X			X	X		X	X		X		X		X		X		X		X		X		
SVC[21]	X	X				X			X				X				X				X		X		
ALSFRS-R (standard)[22]	X	X							X		X		X		X		X		X		X		X		
[redacted]																									

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Doses 4, 5, 6, 7	TC	CV	TC	Dose 8	TC	CV	TC	FU Period[2]				UV
																							CV	TC	Final/ ET Visit	TC	
Days		1		2	8 (±2)	15 (±3)	16 (+1)[4]	22 (±3)	29 (±3)	30 (+1)[4]	36 (±3)	50 (±3)	57, 85, 113, 141 (±3)	58, 86, 114, 142 (+1)[4]	64, 92, 120, 148 (±3)	78, 106, 134, 162 (±3)	169 (±3)[3]	170 (+1)[4]	176 (±3)	177 (+1)[4]	214 (±3)	215 (+1)[4]	259 (±3)	260 (+1)[4]	
Assessments[5]	-28 to -1	Predose	Dosing/Postdose	(24 ±1 h) postdose																					
HHD[21]		X							X				X				X				X		X		
[redacted]																									
Randomization/ Admission to Inpatient Facility		X																							
Study Treatment Administration[23]			X			X			X				X				X								
C-SSRS Questionnaire[24]		X			X	X		X	X		X		X		X		X		X		X		X		X

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Doses 4, 5, 6, 7	TC	CV	TC	Dose 8	TC	CV	TC	FU Period[2]				UV
																						CV	TC	Final/ ET Visit	TC	
Days		1		2	8 (±2)	15 (±3)	16 (+1)[4]	22 (±3)	29 (±3)	30 (+1)[4]	36 (±3)	50 (±3)	57, 85, 113, 141 (±3)	58, 86, 114, 142 (+1)[4]	64, 92, 120, 148 (±3)	78, 106, 134, 162 (±3)	169 (±3)[3]	170 (+1)[4]	176 (±3)	177 (+1)[4]	214 (±3)	215 (+1)[4]	259 (±3)	260 (+1)[4]	
Assessments[5]	**-28 to -1**	**Predose**	**Dosing/Postdose**	**(24 ±1 h) postdose**																					
Clinical Laboratory Samples for Hematology, Coagulation, Blood Chemistry, and Urinalysis[25]	X	X		X		X			X		X		X		X		X		X		X		X		
Serum Sampling for PK[26]		X	X	X	X	X			X				X				X		X						
Blood Sampling for Biomarkers[21]		X							X				X				X				X		X		
[redacted]																									
[redacted]																									
CSF Sampling[29]		X				X			X				X				X		X[30]		X		X		

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Doses 4, 5, 6, 7	TC	CV	TC	Dose 8	TC	CV	TC	FU Period[2]				
																							Final/ ET Visit	TC	UV
Days / Assessments[5]	-28 to -1	1		2	8 (±2)	15 (±3)	16 (+1)[4]	22 (±3)	29 (±3)	30 (+1)[4]	36 (±3)	50 (±3)	57, 85, 113, 141 (±3)	58, 86, 114, 142 (+1)[4]	64, 92, 120, 148 (±3)	78, 106, 134, 162 (±3)	169 (±3)[3]	170 (+1)[4]	176 (±3)	177 (+1)[4]	214 (±3)	215 (+1)[4]	259 (±3)	260 (+1)[4]	
		Predose	Dosing/Postdose	(24 ±1 h) postdose																					
Discharge From Inpatient Facility				X																					
Concomitant Therapy and Procedures Recording		X																							
AE Recording		X																							
SAE Reporting		X																							

[1] Screening assessments can be performed on multiple days (up to 7 days) for ease of participant burden.

[2] Participants in Cohorts D1 and D2 who enter Part 2 after their Treatment Period (after the Day 176 Visit) will not be required to complete the follow-up visits in Part 1 that occur after their enrollment in Part 2. Participants from Cohorts D1 and D2 who do not enter Part 2 will have two follow-up clinic visits and two TCs approximately 6 and 12 weeks after their last dosing visit.

[3] The Part 1 Day 169 Visit may serve as the start of screening period for Part 2. Results from Part 1 Day 169 and Day 176 Visit assessments may be used for the purpose of screening and do not need to be repeated, as long as they are conducted within one month of the Part 2 Day 1 Visit.

[4] TCs that are scheduled for the day after an LP are only required if LP was performed on the previous day.

[5] All clinic visits are expected to take place on site unless participants are unable to travel to the site due to a public health emergency (see Section 16.6)

[6] An informant/caregiver should be available at Screening, and the participation of the same informant/ caregiver for the duration of the study. The informant/ caregiver must provide written informed consent to participate in the study prior to providing any information on either themselves and/or participants.

[7] Including blood samples for HIV, HCV, and hepatitis B virus.

[8] For women of childbearing potential only; to be performed centrally.

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[9] Performed predose on dosing days for women of childbearing potential only; to be performed locally.

[10] To be conducted only in female participants presenting with a history of being postmenopausal to confirm postmenopausal status.

[11] Limited physical examination from Day 8 to Day 259 and UV per the Investigator's discretion.

[12] On dosing days, to be assessed predose and at 3 and 6 hours postdose (±15 minutes). At UV, a limited neurological examination may be performed per the Investigator's discretion.

[13] Day 92 CV only.

[14] On dosing days, ECG and vital signs are to be assessed just prior to drawing PK blood samples at predose, and 2 and 4 hours postdose (±15 minutes). Vital signs may be measured in either the sitting or supine position, and ECGs are to be done in triplicate after resting in the supine position (or semi-recumbent position, if supine is not possible) for ≥ 5 minutes.

[15] During UV, ECGs are to be done if medically indicated. All ECGs will be read by the Investigator at collection and then sent to a central ECG reader for further evaluation and to confirm eligibility at Screening.

[16] Assessments completed on the mobile device include [redacted] the participant ventilation diary. The participant should complete the first set of mobile device assessments in clinic on Day 1. Assessments on the mobile device after Day 1 will be completed on a weekly basis and may be completed at home. Participants should be encouraged to bring the device with them to each study visit.

[redacted]

[19] On Day 1, the participant should complete the ventilation diary in clinic and enter ventilation data for the week prior (i.e., for Days -7 to -1) into the diary on the mobile device. After Day 1, the participant will complete the ventilation diary on the mobile device on a weekly basis.

[20] Study staff should review the participant's ventilation diary with the participant. If there are missing data or discrepancies, the site may document their conversation with the participant as source to supplement the ventilation diary data. For dosing visits, this procedure may be completed up to 24 hours prior to dosing except on Part 1 Day 1, when it should be completed on the dosing day.

[21] When required on dosing days, assessment to be done predose. [redacted] SVC, [redacted] and HHD may be collected up to 24 hours prior to dosing.

[22] Refers to the ALSFRS-R that is administered by a certified evaluator. The evaluator should be blinded to the participant's treatment assignment and to the results of other assessments. To be performed before dosing; may be performed up to 24 hours prior to dosing except on Part 1 Day 1, when it should be administered on the dosing day.

[23] Administered by LP.

[24] Use "Since Last Visit" version of C SSRS from Day 8 onward. At UV may be assessed per the Investigator's discretion.

[25] On dosing days, to be collected before dosing. HbA1c and lipid panel to be assessed at Screening and on Days 1, 85, 176, and 259 only.

[26] To be collected predose and at 1, 2, 4, and 6 hours (±15min) postdose on dosing days. [redacted] or [redacted]

[27] On Day 85 Visit only.

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[redacted]

[29] To be collected predose on dosing days. Collected by LP. [redacted] Participants to be observed in the clinic for ~6 hours after the LP procedure on dosing days and for ~1 hour on nondosing days.

[30] This LP is only done if participant is not entering LTE.

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Table 3: Schedule of Activities Part 2 (all Cohorts)

	Screening[1]	Loading Dose Period						Maintenance Dose Period		Follow Up Period				UV
		Dose 1	TC	Dose 2	TC	Dose 3	TC	Maintenance Dose Visit	TC	CV	TC	Final/ ET Visit	TC	
Days / **Assessments[2]**	**-28 to -1**	**1 (±3)**	**2 (+1)[3]**	**15 (±3)**	**16 (+1)[3]**	**29 (±3)**	**30 (+1)[3]**	**57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, 645, 673, 701, 729, 757, 785, 813, 841, 869, 897, 925, 953, 981, 1009, 1037, 1065, 1093 (±3)**	**1 day after each maintenance dose visit (+1)[3]**	**45d after last dose (+/-3)**	**1 day after Follow-up CV (+1)[3]**	**90d after last dose (+/-3)**	**1 day after Final/ETV (+1)[3]**	
ICF (Main)	X													
ICF (Informant/ Caregiver)	X													
[redacted]														
Confirmation of Eligibility Criteria	X													
Medical History	X	X												
Clinical Laboratory Samples for Viral Serology[4]	X													
Serum Pregnancy Test[5]	X													

	Screening[1]	**Loading Dose Period**						**Maintenance Dose Period**		**Follow Up Period**				
		Dose 1	**TC**	**Dose 2**	**TC**	**Dose 3**	**TC**	**Maintenance Dose Visit**	**TC**	**CV**	**TC**	**Final/ ET Visit**	**TC**	
Days / **Assessments[2]**	**-28 to -1**	**1 (±3)**	**2 (+1)[3]**	**15 (±3)**	**16 (+1)[3]**	**29 (±3)**	**30 (+1)[3]**	**57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, 645, 673, 701, 729, 757, 785, 813, 841, 869, 897, 925, 953, 981, 1009, 1037, 1065, 1093 (±3)**	**1 day after each maintenance dose visit (+1)[3]**	**45d after last dose (+/-3)**	**1 day after Follow-up CV (+1)[3]**	**90d after last dose (+/-3)**	**1 day after Final/ETV (+1)[3]**	**UV**
Urine Pregnancy Test[6]		X		X		X		X		X		X		
FSH Test[7]	X													
Physical Examination[8]	X	X		X		X		X		X		X		X
Neurological Examination (cranial nerves, cerebellar function, motor, and reflexes)[9]	X	X		X		X		X		X		X		X
Weight	X	X						X[10]				X		
Height	X													

	Screening[1]	Loading Dose Period						Maintenance Dose Period		Follow Up Period				
		Dose 1	TC	Dose 2	TC	Dose 3	TC	Maintenance Dose Visit	TC	CV	TC	Final/ ET Visit	TC	
Days / **Assessments[2]**	**-28 to -1**	**1 (±3)**	**2 (+1)[3]**	**15 (±3)**	**16 (+1)[3]**	**29 (±3)**	**30 (+1)[3]**	**57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, 645, 673, 701, 729, 757, 785, 813, 841, 869, 897, 925, 953, 981, 1009, 1037, 1065, 1093 (±3)**	**1 day after each maintenance dose visit (+1)[3]**	**45d after last dose (+/-3)**	**1 day after Follow-up CV (+1)[3]**	**90d after last dose (+/-3)**	**1 day after Final/ETV (+1)[3]**	**UV**
12-Lead ECG[11]	X	X		X		X		X		X		X		X
Vital Signs (temperature, blood pressure, heart rate, respiratory rate)[12]	X	X		X		X		X		X		X		X
Set up study mobile device for Part 2[13]		X												
[redacted]														

	Screening[1]	Loading Dose Period						Maintenance Dose Period		Follow Up Period				
		Dose 1	TC	Dose 2	TC	Dose 3	TC	Maintenance Dose Visit	TC	CV	TC	Final/ ET Visit	TC	
Days / **Assessments[2]**	**-28 to -1**	**1 (±3)**	**2 (+1)[3]**	**15 (±3)**	**16 (+1)[3]**	**29 (±3)**	**30 (+1)[3]**	**57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, 645, 673, 701, 729, 757, 785, 813, 841, 869, 897, 925, 953, 981, 1009, 1037, 1065, 1093 (±3)**	**1 day after each maintenance dose visit (+1)[3]**	**45d after last dose (+/-3)**	**1 day after Follow-up CV (+1)[3]**	**90d after last dose (+/-3)**	**1 day after Final/ETV (+1)[3]**	**UV**
Participant Ventilation Diary[16]		Ongoing weekly collection												
Review ventilation use[17]		X		X		X		X		X		X		
ALSFRS-R (standard)[18]	X	X		X		X		X		X		X		
[redacted]														

	Screening[1]	Loading Dose Period						Maintenance Dose Period		Follow Up Period				
		Dose 1	TC	Dose 2	TC	Dose 3	TC	Maintenance Dose Visit	TC	CV	TC	Final/ ET Visit	TC	
Days / **Assessments[2]**	**-28 to -1**	**1 (±3)**	**2 (+1)[3]**	**15 (±3)**	**16 (+1)[3]**	**29 (±3)**	**30 (+1)[3]**	**57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, 645, 673, 701, 729, 757, 785, 813, 841, 869, 897, 925, 953, 981, 1009, 1037, 1065, 1093 (±3)**	**1 day after each maintenance dose visit (+1)[3]**	**45d after last dose (+/-3)**	**1 day after Follow-up CV (+1)[3]**	**90d after last dose (+/-3)**	**1 day after Final/ETV (+1)[3]**	**UV**
[redacted]														
SVC[19]	X	X		X		X		X		X		X		
[redacted]														

	Screening[1]	Loading Dose Period						Maintenance Dose Period		Follow Up Period				
		Dose 1	TC	Dose 2	TC	Dose 3	TC	Maintenance Dose Visit	TC	CV	TC	Final/ ET Visit	TC	
Days / **Assessments[2]**	**-28 to -1**	**1 (±3)**	**2 (+1)[3]**	**15 (±3)**	**16 (+1)[3]**	**29 (±3)**	**30 (+1)[3]**	**57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, 645, 673, 701, 729, 757, 785, 813, 841, 869, 897, 925, 953, 981, 1009, 1037, 1065, 1093 (±3)**	**1 day after each maintenance dose visit (+1)[3]**	**45d after last dose (+/-3)**	**1 day after Follow-up CV (+1)[3]**	**90d after last dose (+/-3)**	**1 day after Final/ETV (+1)[3]**	**UV**
HHD[19]		X						X[10]				X		
Study Treatment Administration		X[22]		X		X		X						
C-SSRS Questionnaire[19, 23]		X		X		X		X		X		X		X
Clinical Laboratory Samples for Hematology, Coagulation, Blood Chemistry, and Urinalysis[24]	X	X		X		X		X		X		X		
Serum Sampling for PK[19]		X						X[21]						

	Screening[1]	Loading Dose Period						Maintenance Dose Period		Follow Up Period				
		Dose 1	TC	Dose 2	TC	Dose 3	TC	Maintenance Dose Visit	TC	CV	TC	Final/ ET Visit	TC	
Days / **Assessments[2]**	**-28 to -1**	**1 (±3)**	**2 (+1)[3]**	**15 (±3)**	**16 (+1)[3]**	**29 (±3)**	**30 (+1)[3]**	**57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, 645, 673, 701, 729, 757, 785, 813, 841, 869, 897, 925, 953, 981, 1009, 1037, 1065, 1093 (±3)**	**1 day after each maintenance dose visit (+1)[3]**	**45d after last dose (+/-3)**	**1 day after Follow-up CV (+1)[3]**	**90d after last dose (+/-3)**	**1 day after Final/ETV (+1)[3]**	**UV**
Blood Sampling for Biomarkers[19]		X				X		X		X		X		
[redacted]														
CSF Sampling[25]		X		X		X		X		X		X		
Concomitant Therapy and Procedures Recording		Ongoing												X
AE Recording		Ongoing												X

	Screening[1]	Loading Dose Period						Maintenance Dose Period		Follow Up Period				
		Dose 1	TC	Dose 2	TC	Dose 3	TC	Maintenance Dose Visit	TC	CV	TC	Final/ ET Visit	TC	
Days / **Assessments[2]**	**-28 to -1**	**1 (±3)**	**2 (+1)[3]**	**15 (±3)**	**16 (+1)[3]**	**29 (±3)**	**30 (+1)[3]**	**57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449, 477, 505, 533, 561, 589, 617, 645, 673, 701, 729, 757, 785, 813, 841, 869, 897, 925, 953, 981, 1009, 1037, 1065, 1093 (±3)**	**1 day after each maintenance dose visit (+1)[3]**	**45d after last dose (+/-3)**	**1 day after Follow-up CV (+1)[3]**	**90d after last dose (+/-3)**	**1 day after Final/ETV (+1)[3]**	**UV**
SAE Reporting	Ongoing													X

[1] For participants from Cohorts D1 and D2, the Part 1 Day 169 Visit may serve as the start of screening period for Part 2. Results from Part 1 Day 169 and Day 176 Visit assessments may be used for the purpose of screening and do not need to be repeated, as long as they are conducted within one month of the Part 2 Day 1 Visit.
[2] All clinic visits are expected to take place on site unless participants are unable to travel to the site due to a public health emergency (see Section 16.6).
[3] TCs that are scheduled for the day after an LP are only required if LP was performed on the previous day.
[4] Including blood samples for HIV, HCV, and hepatitis B virus.
[5] Only for participants from Cohorts A, B, C1, and C2. For women of childbearing potential only; to be performed centrally.
[6] Performed predose on dosing days for women of childbearing potential only; to be performed locally
[7] To be conducted only in female participants presenting with a history of being postmenopausal and whose postmenopausal status was not already confirmed in Part 1, to confirm postmenopausal status for Part 2.
[8] Limited physical examination from Day 15 onward, and in UV, per the Investigator's discretion.
[9] On dosing days, to be assessed predose and postdose. At UV, a limited neurological examination may be performed at the Investigator's discretion.
[10] To be completed on Day 85, 169, 253, 337, 421, 505, 589, 673, 757, 841, 925, 1009, 1093 Visits only (i.e., every 12 weeks).

[11] ECGs to be assessed predose on dosing days. ECGs are to be done in triplicate after resting in the supine position (or semi-recumbent position, if supine is not possible) for ≥5 minutes. During UV ECGs are to be done if medically indicated. All ECGs will be read by the Investigator at collection and then sent to a central ECG reader for further evaluation and to confirm eligibility at Screening.

[12] Vital signs to be assessed both predose and postdose on dosing days. May be measured in either the sitting or supine position.

[13] Participants from Cohorts D1 and D2 must bring their study mobile device to their Part 2 Day 1 visit. Participants from Cohorts A, B, C1, and C2 will receive their study mobile device on Part 2 Day 1. Assessments completed on the mobile device include [redacted] and the participant ventilation diary. The participant should complete the first set of mobile device assessments for Part 2 in clinic on Part 2 Day 1. Assessments on the mobile device after Day 1 will be completed on a weekly basis and may be completed at home. Participants should be encouraged to bring the device with them to each study visit.

[redacted]

[16] On Part 2 Day 1, the participant should complete the ventilation diary in clinic and enter ventilation data for the week prior (i.e., for Part 2 Days -7 to -1) into the diary on the mobile device. After Day 1, the participant will complete the ventilation diary on the mobile device on a weekly basis.

[17] Study staff should review the participant's ventilation diary with the participant. If there are missing data or discrepancies, the site may document their conversation with the participant as source to supplement the ventilation diary data. For dosing visits, this procedure may be completed up to 24 hours prior to dosing except on Part 2 Day 1, when it should be completed on the dosing day.

[18] Refers to the ALSFRS-R that is administered by a certified evaluator. For participants in Cohorts D1 and D2, during the blinded loading period, the evaluator should be blinded to the participant's treatment assignment and to the results of other assessments. To be performed before dosing; may be performed up to 24 hours prior to dosing, except on Part 2 Day 1, when it should be administered on the dosing day.

[19] When required on dosing days, assessment to be done predose. [redacted] SVC, [redacted] and HHD may be collected up to 24 hours prior to dosing.

[redacted]

[21] Only completed on Day 169, 337, 505, 673, 841, 1009 Visits (i.e., every 24 weeks).

[22] Administered by LP. Participants must not receive their first dose in Part 2 less than 4 weeks after their last dose in Part 1.

[23] Participants from Cohorts D1 and D2 will use "Since Last Visit" version of C-SSRS on Day 1 onward. Participants from Cohorts A, B, C1, and C2 will use the "Since Last Visit" version of the C-SSRS from Day 15 onward. At UV may be assessed per the Investigator's discretion.

[24] On dosing days, to be collected before dosing. Lipid panel and HbA1c to be completed on Screening, Day 1, 85, 169, 253, 337, 421, 505, 589, 673, 757, 841, 925, 1009, 1093 Visits only (i.e., every 12 weeks).

[25] To be collected predose by LP on dosing days. Participants receiving 60mg dose to be observed in the clinic for ~1 hour after the LP procedure. Participants receiving 120mg dose to be observed in the clinic for at least 2 hours after the LP procedure.

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2. LIST OF ABBREVIATIONS

aCSF	artificial cerebrospinal fluid
ADA	anti-drug antibody
AE	adverse event
ALS	amyotrophic lateral sclerosis
[redacted]	[redacted]
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
APTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
ATXN2 [1]	*ataxin-2* gene or RNA
ATXN2 [1]	ataxin-2 protein
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to time of the last measurable concentration
CAA	cytosine-adenine-adenine
CAG	cytosine-adenine-guanine
CMAP	compound muscle action potential
C_{max}	maximum observed concentration
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	clinic visit
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
ECG	electrocardiogram
[redacted]	[redacted]
ET	early termination
FAS	full analysis set
FSH	follicle-stimulating hormone
FUS	fused in sarcoma
GCP	Good Clinical Practice
GD	gestation day
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus

HED	human equivalent dose
HHD	handheld dynamometry
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
ICV	intracerebroventricular
INR	international normalized ratio
[redacted]	[redacted]
IRT	interactive response technology
IT	intrathecal(ly)
LP	lumbar puncture
MAD	multiple-ascending dose
MMSE	Mini-Mental State Examination
mRNA	messenger ribonucleic acid
MRSD	maximum recommended starting dose
NfL	neurofilament light chain
NHP	nonhuman primate
NOAEL	no observed adverse effect level
OLE	open label extension
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
[redacted]	[redacted]
polyQ	polyglutamine
PT	prothrombin time
RNA	ribonucleic acid
[redacted]	[redacted]
SAE	serious adverse event
SC	subcutaneous
SLC22A23 [1]	solute carrier family 22 member 23
SLC25A12 [1]	solute carrier family 25 member 12
SOD1	superoxide dismutase 1
SST	safety surveillance team
SUSAR	suspected unexpected serious adverse reaction
SVC	slow vital capacity
$t_{½}$	elimination half-life
TC	telephone contact
TDP-43	transactive response deoxyribonucleic acid-binding protein 43
T_{max}	time to reach maximum observed concentration
UV	Unscheduled Visit
[redacted]	[redacted]

[1] Based on formatting guidelines (https://www.biosciencewriters.com/Guidelines-for-Formatting-Gene-and-Protein-Names.aspx), references to genes and mRNAs are italicized, and references to proteins are in standard font.

3. INTRODUCTION

BIIB105 is a novel ASO in development for the treatment of ALS and polyQ-ALS.

3.1. Study Rationale

Ataxin-2, encoded by the *ATXN2* gene, is a cytoplasmic RNA-binding protein that has been implicated in the pathology of ALS through several mechanisms, including, but not limited to, cytoplasmic mislocalization of, and aggregation with, other proteins implicated with ALS such as TDP-43. A potential therapeutic approach to indirectly affect TDP-43 is modulation of the ATXN2 protein. While the exact mechanism remains unclear, ATXN2 modulation has been shown to affect TDP-43 toxicity in nonclinical models, where toxicity caused by overexpression of TDP-43 was enhanced with increased expression of ATXN2 and was reduced when ATXN2 levels were depleted [Becker 2017; Elden 2010].

These nonclinical findings linking *ATXN2* to ALS have been supported by human genetic studies and pathological observations in ALS patient tissue. Intermediate-length expansion of the polyCAG region in *ATXN2* has been identified as a significant risk factor for developing ALS [Elden 2010; Neuenschwander 2014; Sproviero 2017]. This repeat region encodes a polyQ segment at the N-terminus of the ATXN2 protein, and when expanded, is believed to stabilize the protein [Elden 2010]. Additionally, retrospective analysis of patients with ALS harboring a polyCAG expanded allele (polyQ patients) as compared with matched patients with ALS harboring normal polyCAG length alleles has shown that patients with ATXN2 polyQ demonstrate faster clinical progression, as measured by the ALSFRS-R and respiratory vital capacity, suggesting that ATXN2 polyQ expansions also confer a risk of more aggressive disease [McMillan 2020]. Finally, ATXN2 protein lacking a polyQ expansion has been found to be aberrantly localized in ~25% of motor neurons in multiple ALS patients [Elden 2010].

BIIB105 is a novel ASO being developed for the treatment of ALS. The ASO targets the *ATXN2*-mRNA for degradation, as a means to decrease ATXN2 protein and thereby mitigate TDP-43 toxicity as seen in nonclinical models.

When delivered systemically, ASOs do not cross the blood-brain barrier at sufficient levels to modulate gene expression in the brain or spinal cord [Agrawal 1991; Broaddus 2000; Cossum 1993]. Thus, to achieve antisense pharmacology in brain or spinal cord, ASOs such as BIIB105 are delivered directly into the CSF space by IT administration.

Given the rapidly progressing, life-threatening, and rare nature of the disease as well as the high unmet medical need in ALS, the first-in-human Phase 1/2 study will be a two-part evaluation of BIIB105 in adult participants with ALS and polyQ-ALS. Part 1 will be a placebo-controlled MAD assessment of the safety, tolerability, pharmacokinetics, pharmacodynamics, and effect on disease progression of BIIB105. Part 2 will be an extension study to assess the long-term safety, tolerability, pharmacokinetics, pharmacodynamics, and effect on disease progression of BIIB105 in participants who complete Part 1 through Week 25 (Day 175 Visit for Cohorts A, B, C1, and C2; Day 176 Visit for Cohorts D1 and D2).

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This study design will minimize the number of participants receiving subtherapeutic doses and/or dosing durations. For all cohorts in Part 1, the 72-hour safety data review following sentinel dosing of the first 2 participants of each dosing cohort and the 7-day safety review for each participant after administration of the first dose and prior to administration of the second dose will allow evaluation of potential acute safety and tolerability findings in each participant prior to the administration of additional doses, similar to a single-ascending-dose study design. Part 2 will provide up to 104 weeks of dosing of BIIB105 for study participants who complete 25 weeks in Part 1. The safety, PK, PD, and clinical function data collected from Part 2 will allow for the understanding of the long-term effect of BIIB105 in participants with ALS and polyQ-ALS.

3.1.1. Rationale for Study Population

This study will be conducted in participants diagnosed with ALS and polyQ-ALS for the following reasons:

- Nonclinical data support the development of BIIB105 in this population.
- Due to the rare, rapidly progressive, and life-threatening nature of ALS that lacks an available cure, there is an urgent need for an effective therapy. The administration of BIIB105 to participants with ALS in the first-in-human study will allow assessment of the safety, tolerability, PK, and potential efficacy of BIIB105 in a relevant population as quickly as possible, while minimizing the number of participants who are exposed to subtherapeutic doses and minimizing the risk to each study participant.
- This study includes a subset of participants with polyQ-ALS as they reflect a subpopulation that carries a genetic risk for developing ALS [Elden 2010; Neuenschwander 2014; Sproviero 2017] and demonstrate faster clinical progression as measured by the ALSFRS-R and respiratory vital capacity [McMillan 2020].

3.1.2. Rationale for Starting Dose and Maximum Exposure

A single-dose NHP toxicity study identified a maximum tolerated dose ([redacted] mg) and reversible AEs at [redacted] mg, which can be monitored clinically. Specifically, 1 of 3 animals dosed at [redacted] mg exhibited increased muscle tone, whole body spasms, and tremors that required administration of diazepam. The animal fully recovered by [redacted] hours. Additional nonclinical NHP data was obtained from a 13-week study with [redacted] doses of BIIB105 administered at [redacted] mg and a 41-week study with [redacted] doses of BIIB105 administered at [redacted] mg.

BIIB105 was tested in 2 pharmacologically relevant species: NHP and mouse. Because BIIB105 produced no adverse effects at any of the dose levels used in the [redacted] repeat-dose GLP studies, the highest dose of each study was identified as the NOAEL. Specifically, the NOAEL for the 13-week monkey IT study is [redacted] mg, the NOAEL for the 41-week monkey IT study is [redacted] mg, the NOAEL for both the 14-week and 26-week mouse SC studies is [redacted] mg/kg, and the NOAEL for the 57-day mouse ICV study is [redacted] mg. The NHP was deemed the most sensitive species because dose-limiting effects were identified in a GLP single-dose NHP study at [redacted] mg, whereas no

dose-limiting toxicities have been identified in the rodent studies. At the time of selection of the starting dose for this study, the 13-week NHP study also provided the lowest HED, which was calculated to be [redacted] mg utilizing a CSF volumetric scaling factor of 10. This represented the most conservative estimate based on CSF volume ratio between humans and NHPs and as compared with the HED in the mouse ICV ([redacted] mg) and mouse SC ([redacted] mg or [redacted] mg/kg based on a 60 kg human) toxicity studies.

Therefore, the selection of the starting dose for Part 1 of this study is based on the NOAEL dose of [redacted] mg, established in the 13-week toxicology study in cynomolgus monkeys, and on the expected PD of BIIB105 in the brain cortex and spinal cord. The HED value was divided by the conventional safety factor of 10 to yield the MRSD of [redacted] mg. The proposed [redacted] mg starting dose is below the MRSD, has a [redacted]-fold safety factor over the HED ([redacted] mg) of the NOAEL from the 13-week toxicology study, and is expected to produce minimal to moderate pharmacologic effects in the brain and spinal cord.

There were 2 chronic toxicology GLP studies conducted to support the dosing duration for Part 2 of this study. In the 41-week NHP study BIIB105 was administered IT ([redacted] mg) on Days [redacted], then [redacted] until Day [redacted]. In the 26-week mouse study BIIB105 was administered SC ([redacted] mg/kg/dose) every [redacted] from Day [redacted] through Day [redacted]. NOAEL for both of the studies was considered to be the highest dose tested. The 41-week NHP chronic toxicology study provided the lowest HED, which was calculated to be [redacted] mg utilizing a CSF volumetric scaling factor of 10. These chronic toxicology studies support the proposed dose levels and dosing duration in the study.

A physiologically based PK model was used to establish the expected relationship between IT doses of BIIB105 and its concentrations in various brain regions. The potency of BIIB105 determined in transgenic mouse studies was used to project expected mRNA lowering in humans. The potency of BIIB105 is anticipated to be higher in the spinal cord than brain, with reported concentrations at [redacted]% of maximum observed biologic effect of [redacted] µg/g and [redacted] µg/g in the brain cortex and spinal cord, respectively. Results from a TDP-43 transgenic mouse model of ALS suggest a dose-dependent increase in survival with decreasing levels of *ATXN2*. It was shown that in TDP-43 transgenic mice, ASO induced reduction of *ATXN2* mRNA levels in CNS tissues by [redacted]% on average and resulted in a [redacted]% increase in median lifespan compared with control ASO littermates [Becker 2017]. An mRNA reduction of approximately [redacted]% is therefore considered the target BIIB105 PD effect in humans that could be indicative of potential clinical efficacy.

The predicted *ATXN2* mRNA reductions in the target CNS regions and safety margins at steady state at the proposed dose levels planned in this study are shown in Table 4. The MRSD of [redacted] mg is estimated to reduce *ATXN2* mRNA levels approximately [redacted]% in the cortex and approximately [redacted]% in the spinal cord after reaching steady state. In consideration of the higher reduction of *ATXN2* mRNA in the spinal cord, a starting dose of [redacted] mg is proposed, which is anticipated to reduce *ATXN2* mRNA levels by approximately [redacted]% in the cortex and [redacted]% in the spinal cord. A maximum dose of [redacted] mg is proposed at this time and is estimated to reduce *ATXN2* mRNA levels in the cortex by approximately [redacted]% and in the spinal cord by approximately [redacted]% at steady state and will provide an approximately [redacted]-fold safety margin to

the HED ([redacted] mg) of the 13-week NHP IT toxicology study NOAEL ([redacted] mg) and an approximately [redacted] fold safety margin to the HED ([redacted] mg) of the 41-week NHP IT toxicology study NOAEL [redacted] mg). Postmortem tissue analyses from the 13-week and 41-week toxicology studies in NHP showed that the CNS tissue ATXN2 protein levels are reflective of CNS tissue *ATXN2* mRNA levels. [redacted]

The length of the dosing interval during the 28-day loading period (3 doses administered once every 2 weeks) is designed to yield a rapid onset of steady-state exposure by the third dose on Day 29. Following the loading period, dosing every 4 weeks is projected to maintain steady-state exposure based on the whole-body physiologically based PK model.

Table 4: Predicted *ATXN2* mRNA Reduction (Cortex and Spinal Cord), ATXN2 protein reduction (CSF), and Safety Margins at Steady-state at Proposed Dose Levels

Dose (mg)	Fold Increase	% Decrease in Cortex Average (maximum)	% Decrease in Spinal Cord Average (maximum)	% Decrease in CSF (approximate median)	Safety Margin[1] 13 week/ 41 week
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] Safety margins are based HED of the NOAEL 13 week and 41 weeks NHP IT toxicology studies using CSF volumetric scaling.

During Part 1 of the study, the SST will review safety, tolerability, and available PK data before each dose escalation. Further detail regarding the process for evaluation of data to support dose escalation decisions is provided in Section 5.3 . If the emerging data reveal substantial differences in safety findings or drug exposure from nonclinical or modeling and simulation data, the dose levels may be adjusted, and cohorts may be expanded or added at intermediate doses. If adjustments to dose levels are needed based on review of emerging PK data, dose escalations will not exceed 2× when above MRSD. The Sponsor will submit a substantial protocol amendment if dose escalation above [redacted] mg is warranted.

3.1.3. Rationale for the Collection of Genetic Samples

Genetic polymorphism in genes encoding drug targets or the downstream pathways, as well as proteins that affect drug absorption, distribution, metabolism, and elimination, may affect the safety and efficacy of the study treatment.

PolyQ intermediate repeat mutation analysis will be required to screen for participant inclusion in Cohorts C2 and D2. Additionally, for this compound, genetics may influence success in this

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participant population. Access to utilize these samples for future analyses may help further ALS research.

3.2. Background

3.2.1. Overview of ALS

ALS is a rare neurodegenerative disease resulting in pathologic loss of motor neurons and their axons within the cortex, brainstem, spinal cord, and peripheral nerves. Patients suffer from progressive loss of muscle mass, strength, and function in bulbar, respiratory, and voluntary muscles. ALS is formally defined by clinical history and examination that demonstrate loss of both upper and lower motor neuron function over time. Functional decline and death, typically from respiratory failure, are inevitable and occur approximately 2 to 5 years from disease onset unless tracheostomy and mechanical ventilation are elected to support life.

A hallmark of ALS pathogenesis in the majority of patients is the presence of cytoplasmic inclusions containing aggregated TDP-43 in motor neurons [Ling 2013; Neumann 2006]. TDP-43 is a ubiquitously expressed protein that plays a variety of roles in RNA processing. Mutations in the *TDP-43* gene have been shown to cause familial ALS; however, most patients do not carry an associated *TDP-43* genetic mutation, suggesting that abnormal cytoplasmic aggregation of the wild-type protein may play a role in disease pathogenesis [Scotter 2015a, 2015b].

3.2.2. Current Therapies for ALS

Available treatments for ALS include riluzole, edaravone, and sodium phenylbutyrate and taurursodiol, with approvals varying by region. Each has demonstrated modest effects on disease progression.

Riluzole provides a modest increase in survival (2 to 3 months) without noticeable improvement in strength or disability [Miller 2012]. The mode of action of riluzole is unknown, but its pharmacological activities include inhibition of glutamate release, inactivation of voltage-dependent sodium channels, and interference with intracellular events that follow neurotransmitter binding at excitatory amino acid receptors.

In a 6-month randomized study, Japanese patients with early-stage ALS receiving edaravone demonstrated a decreased decline in ALSFRS-R scores as compared with patients who received placebo [Writing Group and Edaravone (MCI-186) ALS 19 Study Group 2017]. The mechanism of action of edaravone in ALS is unknown.

In a 6-month randomized study in the United States, patients with ALS who received a combination of sodium phenylbutyrate and taurursodiol demonstrated less decline in ALSFRS-R scores over 24 weeks compared with patients who received placebo [Paganoni 2020]. The mechanism of action of sodium phenylbutyrate in ALS is unknown, but its pharmacological activities include histone deacetylase inhibition and upregulation of heat shock proteins. The

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mechanism of action of taurursodiol in ALS is also unknown, but its pharmacological activities include reduction of mitochondrial permeability.

3.2.3. Profile of Previous Experience with BIIB105

See the Investigator's Brochure for detailed information on relevant nonclinical and clinical studies. This is a first-in-human study.

3.2.3.1. Nonclinical Experience

The potency and selectivity of BIIB105 for the reduction of *ATXN2* mRNAs have been investigated using in vitro and in vivo pharmacology studies. Treatment with BIIB105 was found to potently reduce *ATXN2* mRNA and protein levels in human cellular models and animal models of mice and NHPs. Binding site analysis showed that BIIB105 targets an exonic sequence common to all *ATXN2* mRNAs and has perfect complementarity to human, mouse, rat, and monkey *ATXN2*. The BIIB105 binding site contains no validated variations with frequency > [redacted]% from the human reference genome. Treatment with murine *Atxn2* ASO resulted in a significant benefit in survival and improvement in motor performance in a murine model of TDP-43-dependent toxicity. *Atxn2* mRNA levels were reduced by approximately [redacted]% to [redacted]% in the CNS of these treated mice. A dose-dependent reduction in ATXN2 protein was detected in the spinal cord and cerebellum from treated relative to untreated transgenic mice that expressed human ATXN2 protein with polyQ length of [redacted]. Multiple administrations of BIIB105 in NHPs resulted in a significant and dose-dependent reduction of *ATXN2* mRNA and protein in all tissues tested. After the recovery period, *ATXN2* mRNA and protein knockdown persisted in all tissues but had begun to return to baseline levels.

BIIB105 was also found to have selectivity for *ATXN2* mRNAs relative to other human transcripts. Off-target gene analysis showed that BIIB105 was partially ([redacted] mismatches) complementary to [redacted] human genes, [redacted] of which are not expressed appreciably in human tissues. Of the remaining [redacted] genes, only [redacted], *SLC25A12* and *SLC22A23*, showed consistent reduction following BIIB105 treatment. BIIB105 was determined to be [redacted] fold or more selective for *ATXN2* than for *SLC25A12* and *SLC22A23*, respectively, in A-431 cells. In vivo BIIB105 testing in NHPs resulted in a significant and dose-dependent reduction of *SLC25A12* mRNA in all tissues tested. However, the extent of *ATXN2* mRNA knockdown was universally greater than that of *SLC25A12* mRNA at all doses and in all tissues tested.

Following IT administration in NHPs (which are well accepted to have ASO PK parameters that are highly predictive of those in humans), BIIB105 concentrations in CSF declined in a multiphasic manner, with a rapid distribution phase (which dominated the clearance from CSF), followed by a slower and longer elimination phase. The rapid distribution phase is due to rapid and broad distribution from CSF to CNS tissues with additional clearance due to transfer to systemic circulation. BIIB105 concentrations in serum peaked [redacted] after the IT bolus injection and then rapidly declined during the first [redacted] after dosing, followed by a much slower elimination phase. The rapid decline from serum is likely due to extensive distribution to systemic tissues.

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Following SC administration in mice, BIIB105 is rapidly and extensively distributed from serum to liver and kidney. BIIB105 concentrations in serum peaked [redacted] after dosing, indicating rapid absorption into the systemic circulation.

Dose-dependent tissue distribution of BIIB105 was seen in all repeat-dose toxicology studies with no clear or consistent evidence of a sex difference in distribution to tissues. After IT administration in monkeys, BIIB105 distributed broadly to CNS tissues. Relatively high concentrations were observed in the liver and kidneys, indicating that a significant proportion of the administered dose was distributed from CSF to the systemic circulation. A similar systemic distribution profile was observed following ICV administration in mice.

Nonclinical evaluation of BIIB105 metabolites has not yet been conducted; however, based on previous experience with similar classes of ASOs [redacted], BIIB105 metabolites are expected to be consistent with nuclease-mediated metabolism. In vitro or in vivo drug-drug interaction studies have not been conducted; however, based on previous experience, BIIB105 is not expected to be a substrate for cytochrome P450-mediated oxidative metabolism and therefore should not compete with other drugs for this metabolic pathway [Geary 2003; Yu 2007].

Nonclinical evaluation of the urinary excretion of BIIB105 has not been performed. The metabolism of similar classes of ASOs in tissues has been reported to be slow, followed by urinary excretion of mainly metabolites, with a minor component of the administered compound excreted as parent [Geary 2003; Post 2019]. A similar disposition is expected for BIIB105.

Nonclinical toxicity of BIIB105 was assessed after single- and repeat-dosing studies were conducted in mice and NHPs, the latter being deemed as the most relevant species.

In the 5 GLP repeat-dose studies in mice and NHPs, BIIB105 produced no adverse effects at any of the dose levels used in each study. The NOAEL for the 13-week NHP IT study is [redacted] mg, the NOAEL for the 41-week NHP IT is [redacted] mg, the NOAEL for both the 14-week and 26-week mouse SC study is [redacted] mg/kg, and the NOAEL for the 57-day mouse ICV study is [redacted] mg. A single-dose NHP toxicity study identified a maximum tolerated dose ([redacted] mg) and reversible AEs at [redacted] mg that can be monitored and controlled clinically. These doses correspond to HED values of [redacted] mg and [redacted] mg, respectively, based on CSF volume scaling in the most sensitive species.

Central administration of BIIB105 in mice ([redacted] ICV doses over 57 days) or NHP ([redacted] IT doses over 13 weeks and [redacted] IT doses over 41 weeks) produced no CNS adverse effects. In NHPs, BIIB105-related CNS effects included transient decreases of spinal reflexes and postural reactions in individual animals after each dosing session. Due to the transient nature and lack of persistent impact to ambulatory function, these reduced or absent spinal reflexes were considered nonadverse, with no histopathologic correlates to these findings. One animal in the 41-week NHP study at the [redacted] mg dose level had more persistent head-holding, tremors, and abnormal general attitude which did not affect the animal's functionality. This animal additionally had systemic and CNS inflammatory changes with an AUC-time curve exposure comparable to the [redacted] mg dose level and a high accumulation without evidence of neuronal necrosis or degeneration on histopathology. The clinical and histopathologic findings in this animal were nonadverse.

Repeated central administration of BIIB105 produced nonadverse microscopic changes in both mice and NHPs. Micro- and/or macro-vesicular neuronal vacuolation were noted in CNS tissues as well as in multiple systemic tissues in NHP. Nonadverse vacuolar findings were of low severity and had no associated neuronal degeneration or necrosis/apoptosis or correlating clinical signs. Macrovesicular neuronal vacuolation has been observed for IT-administered ASOs, which was attributable to the tissue fixation in the presence of drug (Ionis Study 396443-AS11 and Biogen Study No. PD17-12).

Repeated systemic administration of BIIB105 in mice resulted nonadverse microscopic effects related to BIIB105 including macrophage vacuolation in multiple tissues, tubular basophilic granules in the kidney, decreased erythroid cellularity of the bone marrow, tubular vacuolation in the kidney, increase in incidence of hematopoiesis in the spleen, and increase in incidence of decreased lymphoid cellularity in the thymus. These changes were considered nonadverse based on their minimal to mild severity, lack of clinical pathology correlate, and/or absence of function impairment. Kidneys are a known target organ for nonspecific, ASO-associated histopathologic changes due to the preferential uptake of ASOs by proximal tubular epithelium and processing within endosomes and lysosomes [Henry 2008; Monteith 1999].

The macrophage vacuolation noted in multiple tissues in both the NHP (IT) study and mouse (SC) study was considered to be class-related effects of ASO compounds. Cytoplasmic vacuolation of macrophages has been reported to reflect lysosomal accumulation of oligonucleotides [Braendli-Baiocco 2017] or cellular activation and cytokine production without oligonucleotide accumulation [Frazier 2015] and is not considered to be adverse because impairment of function has not been reported [Lenz 2018].

In NHPs, the transient mild increases in complement Bb fragment, sC5b-9, and C3a observed following dosing were consistent with the well-documented proinflammatory effects of ASO treatment in NHPs [Engelhardt 2015; Henry 2014]. Nonadverse elevated C-reactive protein concentration in individual animals with mild increases in fibrinogen reflected acute phase reactions that were mostly mild and generally not associated with clinical signs, neurological deficits, or histopathologic findings.

BIIB105 is not a genotoxicant as negative results were observed in the bacterial reverse mutation, in vitro chromosomal aberration, and in vivo rat micronucleus assays at limit concentrations/doses.

In a fertility study, there were no BIIB105-related effects on sperm concentration or morphology in male mice. In female mice, there were no BIIB105-related effects on female reproductive parameters, estrous cycle length, or precoital intervals. The NOAEL for reproductive toxicity was [redacted] mg/kg/dose. The corresponding serum exposure was a mean C_{max} of [redacted] µg/mL and a mean AUC_{0-24} of [redacted] µg*h/mL after repeat dosing in males. The exposures in pregnant females were a mean C_{max} of [redacted] µg/mL and a mean AUC_{0-24} of [redacted] µg*h/mL on GD 14.

In mice, BIIB105 did not result in any effects on embryo-fetal survival. A statistically significantly lower mean fetal weight was observed at [redacted] mg/kg/day and was considered adverse. BIIB105 did not produce any fetal external, visceral, or skeletal malformations or variations in

mice. The NOAEL for developmental toxicity in mice was considered to be [redacted] mg/kg/dose, which corresponded to a mean C_{max} of [redacted] µg/mL and a mean AUC_{0-24} of [redacted] µg*h/mL in females. Fetal exposure, based on BIIB105 concentrations in liver, was approximately [redacted] times lower than the maternal C_{max}.

A dose level of [redacted] mg/kg/dose was considered to be the NOAEL for maternal toxicity and embryo-fetal development when BIIB105 was administered via SC injection to New Zealand White rabbits. This dose level was associated with a mean serum C_{max} of [redacted] µg/mL and a mean AUC_{last} of [redacted] µg*h/mL on GD [redacted]. There was no detectable BIIB105 in fetal livers in rabbit.

3.2.3.2. Clinical Experience

This is the first-in-human study of BIIB105. Emerging clinical data can be found in the Investigator's Brochure.

3.3. Benefit-Risk Assessment

The potential benefit of BIIB105 in ALS has not been established. This study has been designed with appropriate dose escalation, safety monitoring, and stopping rules to minimize risks to participants. The results of this study may offer key insights into the development of a disease-modifying therapy for ALS.

This is a first in human study, thus the risk in humans is unknown. Emerging clinical data can be found in the Investigator's Brochure.

Nonclinical work with *Atxn2* homozygous knockout mice suggests that ATXN2 reduction could be associated with risks of metabolic complications (adult-onset obesity and insulin resistance) and subtle neurological deficits [Huynh 2009; Kiehl 2006; Lastres-Becker 2008]. Human data from the Genome-Wide Association Studies database suggest that variation in *ATXN2* could be associated with changes in blood pressure and cardiometabolic phenotypes [Auburger 2014]. From the nonclinical safety studies in NHPs, the adverse effect level was considered to be [redacted] mg based on severe but reversible and monitorable clinical signs: 1 of 3 animals exhibited increased muscle tone, whole body spasms, and tremors that required administration of diazepam. The animal fully recovered by [redacted] hours. No adverse metabolic effects were seen in toxicology studies. Participants will be monitored in the clinical setting with neurological and physical examinations and careful monitoring of blood chemistries, among other safety assessments.

Although LP is generally considered a safe procedure, certain complications can occur in a subset of patients. These may include, but are not limited to, back pain, headache, nausea, infection, bleeding, radicular pain and numbness, and bruising or injury at the injection site. These potential risks can be mitigated by using atraumatic needles, avoiding contraindicated medications, and testing coagulation and platelet counts prior to the procedure. Importantly, life-threatening cerebral herniation is a possible complication of a lumbar puncture procedure.

Reproductive toxicity studies were conducted in mice and rabbits using SC administration of BIIB105 once every other day. In a definitive combined fertility and embryo-fetal development

study in male and female mice, there was no effect of BIIB105 on fertility in either sex. BIIB105 did not produce any fetal external, visceral, or skeletal malformations or variations in mice or rabbits. However, there were BIIB105-related effects on embryo-fetal development in both species. In mice, there were lower mean fetal body weights that were considered adverse at the highest dose tested ([redacted] mg/kg). In a dose-range finding study in rabbits, dose-limiting BIIB105-related findings included body weight losses, reduced food consumption, and abortions. There was very limited fetal exposure in mice only, with concentrations of BIIB105 detected in fetal mouse liver approximately [redacted]-fold lower than the maternal C_{max}. Due to these adverse findings in the reproductive toxicity nonclinical studies, all men and women of childbearing potential must use highly effective contraception during the study and for at least [redacted] after the study (for female participants) and at least [redacted] after the study (for male participants).

ALS is a debilitating, rapidly progressing, and life-threatening disease with a high unmet need for effective therapies. Overall, the benefit-risk profile is positive for the continued clinical development of BIIB105 for the treatment of ALS and polyQ-ALS.

4. STUDY OBJECTIVES AND ENDPOINTS

Part 1

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.	Incidence of AEs and SAEs in Part 1.
Secondary Objective	**Secondary Endpoints**
To assess the PK profile of BIIB105 in serum and CSF of participants with ALS or polyQ-ALS.	Serum and CSF concentrations of BIIB105 in Part 1. To evaluate the following serum PK parameters in Part 1: • AUC_{inf} • AUC_{last} • C_{max} • T_{max} • $t_{½}$
To evaluate the biomarker effect of BIIB105 in participants with ALS or polyQ-ALS.	Secondary biomarker measure: • Changes from baseline in plasma levels of NfL in Part 1
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the PD effect of BIIB105 in participants with ALS or polyQ-ALS.	Exploratory PD measure: • Change from baseline in CSF levels of ATXN2 protein in Part 1.
[redacted]	

Part 2

Primary Objective	Part 2 Primary Endpoint
To evaluate the long-term safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.	Incidence of AEs and SAEs in Part 2.

Integrated Part 1 and Part 2

Primary Objective	**Primary Endpoint**
To evaluate the long-term safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.	Incidence of AEs and SAEs during the BIIB105-treated period in Part 1 and/or Part 2.
Secondary Objective	**Secondary Endpoints**
To assess the long-term PK profile of BIIB105 in serum and CSF of participants with ALS or polyQ-ALS.	Serum and CSF concentrations of BIIB105 in Part 1 and Part 2. • CSF trough PK concentration • Serum PK concentration if available
To evaluate the long-term biomarker effect of BIIB105 in participants with ALS or polyQ-ALS, and, where relevant, to assess the impact of earlier initiation of BIIB105 (i.e., at start of Part 1) compared with delayed initiation of BIIB105 (i.e., at start of Part 2) on biomarkers.	Secondary biomarker measure: • Changes from Part 1 baseline (Cohorts D1, D2) or Part 2 baseline (Cohorts A, B, C1, C2) in plasma levels of NfL
To evaluate the long-term effect of BIIB105 on measures of clinical function and, where relevant, to assess the impact of earlier initiation of BIIB105 (i.e., at start of Part 1) compared with delayed initiation of BIIB105 (i.e., at start of Part 2) on measures of clinical function.	Changes from Part 1 baseline (Cohorts D1, D2) or Part 2 baseline (Cohorts A, B, C1, C2) in the following assessments: • SVC • ALSFRS-R score • Muscle strength, as measured by HHD Survival analyses: • Time to death or permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days)

	• Time to death • Time to death, incorporating post-study withdrawal or study completion vital status data
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the long-term PD effect of BIIB105 in participants with ALS or polyQ-ALS, and, where relevant, to assess the impact of earlier initiation of BIIB105 (i.e., at start of Part 1) compared with delayed initiation of BIIB105 (i.e., at start of Part 2) on the PD measure.	Exploratory PD measure: • Change from Part 1 baseline (Cohorts D1, D2) or Part 2 baseline (Cohorts A, B, C1, C2) in CSF levels of ATXN2 protein.
[redacted]	

This study collects samples that under separate optional consent may be used for future scientific and genetic research. Objectives related to this future research have not been determined.

5. STUDY DESIGN

5.1. Study Overview

5.1.1. Part 1

Part 1 is a Phase 1/2, randomized, double-blind, placebo-controlled, MAD evaluation of the safety, tolerability, and PK of BIIB105, administered IT to approximately 98 participants (76 participants with ALS and 22 participants with polyQ-ALS) at approximately 15 sites globally. Cohorts A, B, C1, and C2 will receive up to 5 doses over approximately 3 months. Cohorts D1 and D2 will receive up to 8 doses over approximately 6 months.

Approximately 98 participants are planned to be randomized in Part 1. Participants who withdraw may be replaced in a cohort at the discretion of the Sponsor. With potential replacement, approximately 108 participants could be randomized.

Adult participants with ALS will be randomized at a ratio of 3:1 (active drug:placebo) in Cohorts A, B, C1, and D1. Adult participants with polyQ-ALS will be randomized at a ratio of 3:1 in Cohort C2 and at a ratio of 2:1 in Cohort D2. Cohorts C1 and C2 can dose concurrently. Cohorts D1 and D2 can dose concurrently.

If dosing stops at one of the lower dosing cohorts, the cohort with the highest tolerated dose may be expanded to include an additional 20 participants with ALS (3:1, active drug:placebo) and an additional 18 participants with polyQ-ALS (2:1, active drug:placebo).

The first 2 participants in all cohorts, except cohort C2, will be randomized at a ratio of 1:1 (active drug:placebo) and dosed as a sentinel group. No other participants within the cohort will be dosed until the Investigators have reviewed 72 hours of safety data after dosing the first 2 participants and communicated with the Sponsor Medical Director and Global Medical Safety Physician. Based on this safety evaluation, the Sponsor will determine if the rest of the cohort can be dosed. For the remainder of participants in all cohorts, except for cohort C2, no more than 2 participants will receive their first dose of study treatment on the same day throughout the study. For cohort C2, the participants will be randomized 3:1 (active drug:placebo). Treatment will be staggered by 72 hours for the first 2 participants. The first 2 participants will be dosed as a sentinel group, and no other participant will be dosed until the Investigators have reviewed safety data after dosing the first 2 participants and communicated with the Sponsor Medical Director and Global Medical Safety Physician. This phone call will occur 72 hours after the dosing of the second participant. Based on this safety evaluation, the Sponsor will determine if the rest of the cohort can be dosed. If approved, the third and fourth participants may receive their first dose of study treatment on the same day.

For each participant, a review of all available safety and tolerability data will be performed approximately 7 days after the first dose is administered and before administration of the second dose on Day 15. This single-dose review will be performed by the site's Principal Investigator or

designee and communicated to the Sponsor Medical Director and Global Medical Safety Physician, or their appropriate designees. The Sponsor Medical Director and Safety Physician will determine if each participant can proceed with subsequent doses. The second dose cannot be administered until this review is complete.

Randomization will be performed using IRT. See Figure 1 for a schematic of the study design.

5.1.2. Part 2

Part 2 is an open-label evaluation of BIIB105 administered IT to participants with ALS and polyQ ALS who have completed Part 1 through Week 25 (Day 175 Visit for Cohorts A, B, C1, C2; Day 176 Visit for Cohorts D1, D2).

Participants will receive up to approximately 41 doses in Part 2. Two dose levels will be administered – participants from Part 1 Cohorts A, B, C1, and C2 will receive 60 mg BIIB105; participants from Part 1 Cohorts D1 and D2 will receive 120 mg BIIB105.

In Part 2, the 60 mg dose may be increased, at the Sponsor's discretion, to doses up to 120 mg. Before increasing the dose level, the SST must review safety and PK data for Cohorts D1 and D2 (Part 1) and there must be agreement that the current emerging safety, tolerability, and PK data support the dose increase. Doses in Part 2 may also be decreased at the Sponsor's discretion at any time during the study.

5.2. Study Duration for Participants

5.2.1. Study Duration for Participants in Part 1

The total Part 1 study duration for each participant in Cohorts A, B, C1, and C2 will be approximately 29 weeks:

- Screening Period of up to 4 weeks
- Treatment Period of 13 weeks
- Follow-up Period of approximately 12 weeks

Participants in Cohorts A, B, C1, and C2 will have up to 13 CVs and 9 TC during the study, which include at least 1 Screening Visit, 5 Dosing Visits of which the first dose will require an inpatient stay of 2 days, 7 Follow-up Visits, and 9 TC. All visits should be performed within the number of days from the nominal visit day, specified in Section 1. Visit days are calculated with respect to Day 1 (the date of first dose).

The total Part 1 study duration for each participant in D1 and D2 will be between approximately 29 and 41 weeks:

- Screening Period of up to 4 weeks

- Treatment Period of 25 weeks
- Follow-up Period of approximately 12 weeks (only completed if the participant does not enter Part 2 after the Treatment Period)

Participants in Cohorts D1 and D2 will have up to 19 CVs and 15 TCs which will include at least 1 Screening Visit, 8 Dosing Visits of which the first will require an inpatient stay of 2 days, up to 10 Follow-up Visits, and up to 15 TCs.

Participants in Cohorts D1 and D2 who enter Part 2 after their Treatment Period (after the Day 176 Visit) will not be required to complete the follow-up visits in Part 1 that occur after their enrollment in Part 2. Participants from Cohorts D1 and D2 who do not enter Part 2 will have two follow-up clinic visits and two TCs approximately 6 and 12 weeks after their last dosing visit.

Of note, if the Study Sponsor decides to terminate Part 1 without terminating Part 2, participants who are active in Part 1 at the time of the Sponsor's decision will have the opportunity to end Part 1 and screen and enroll into Part 2 prior to completing Week 25.

5.2.2. Study Duration for Participants in Part 2

Study duration for each participant in Part 2 will be up to approximately 172 weeks:

- Screening Period of up to 4 weeks (for participants from Cohorts D1 and D2, Screening Period begins with Day 169 Visit of Part 1)
- Treatment Period of up to approximately 156 weeks: either 104 weeks, OR until the last participant enrolled has had the opportunity for their Part 2 Day 365 visit (Week 52), whichever occurs later
- Follow-up Period of approximately 12 weeks

Participants will have up to approximately 44 CVs and 43 TCs during Part 2 of the study, which will include at least 1 Screening Visit, up to approximately 41 Dosing Visits, 2 Follow-Up Visits, and up to 43 TCs.

The end of study date for a participant may be the last study visit, last follow-up TC, or last protocol-specified assessment, or if the participant has ongoing AEs that are being followed up, the date may be the date of AE resolution.

After a participant's end of study date, follow-up on vital status and date of death (if deceased) will be performed for participants who provide optional consent for data collection after study completion.

5.3. Dosing

5.3.1. Dose Escalation (Part 1)

For each dose escalation, safety (AEs/SAEs, vital signs, ECGs, and laboratory parameters) and available PK data will be reviewed. The proposed dose escalation is illustrated in Figure 1 and the proposed dosing groups are as follows:

Participants with ALS:

Cohort A: BIIB105 5 mg (6 participants) or placebo (2 participants)

Cohort B: BIIB105 20 mg (6 participants) or placebo (2 participants)

Cohort C1: BIIB105 60 mg (9 participants) or placebo (3 participants)

Cohort D1: BIIB105 120 mg (approximately 36 participants) or placebo (approximately 12 participants)

Participants with polyQ-ALS:

Cohort C2: BIIB105 60 mg (3 participants) or placebo (1 participant)

Cohort D2: BIIB105 120 mg (approximately 12 participants) or placebo (approximately 6 participants)

See Section 3.1.2 for details regarding the rationale for the starting dose and dose escalation.

After a cohort (Cohorts A, B, C1, and C2) is fully randomized and at least 36 days have elapsed since the randomization and dosing of the eighth participant, a Sponsor SST will hold a dose escalation meeting to review all available blinded safety data from all randomized participants. There must be a minimum of 6 evaluable participants for the dose escalation meeting to occur. In Cohort C2, all 4 participants must be evaluable for the dose escalation meeting to occur. Evaluable participants are defined as those who have completed 3 dosing visits and the Day 36 CV. This CV occurs 1 week after the Day 29 dose, the dose that is projected to result in the targeted steady-state exposures for the cohort. Dosing of Cohort D1 is dependent on the SST approving the safety of Cohort C1, and dosing of Cohort D2 is dependent on an SST approving the safety of Cohort C2.

For Cohort D1, the safety review will occur after the cohort is fully randomized, and at least 92 days have elapsed since the randomization and dosing of the 36th participant. The SST will review all available blinded safety data from all randomized participants in the cohort, which must include a minimum of 33 evaluable participants (those who completed all of the first 5 dosing visits as well as the Day 92 clinic visit). This review will be for a final safety review for Cohort D1. Should Part 1 be terminated early (per Section 5.2.1 and Section 13.4) prior to reaching randomization of the entire D1 cohort or minimal evaluable criteria as defined, a final

safety SST will be held for Cohort D1 with all available safety data at the time of Part 1 termination.

For Cohort D2, the safety review will occur after the cohort is fully randomized, and at least 92 days after the randomization of the 15th participant. The SST will review all available blinded safety data from all randomized participants in the cohort, which must include a minimum of 12 evaluable participants (those who completed all of the first 5 dosing visits as well as the Day 92 clinic visit). This review will be for a final safety review for Cohort D2. Should Part 1 be terminated early (per Section 5.2.1 and Section 13.4) prior to reaching randomization of the entire D2 cohort or minimal evaluable criteria as defined, a final safety SST will be held for Cohort D2 with all available safety data at the time of Part 1 termination.

Cohorts D1 and D2 can be reviewed concurrently or in separate SSTs, depending on when the cohorts have reached the minimum evaluable patients.

Principal Investigators from sites where participants were dosed will be included in the blinded safety data review. Review of blinded safety data may be followed by review of unblinded safety data of the current and preceding cohorts by the SST. Details of the unblinded review as well as the personnel to be unblinded to support dose escalation will be clearly defined in the Dose Escalation Plan and Unblinding Plan for this study.

In addition to the review of all safety data, there will be a review of available PK data collected through the third dose prior to dosing of the next dose cohort for Cohorts A, B, C1, and C2. For Cohort D1, there will be a review of all available PK data for a minimum of 33 evaluable participants. For Cohort D2, there will be a review of all available PK data for a minimum of 12 evaluable participants. Should Part 1 be terminated early (per Section 5.2.1 and Section 13.4) prior to reaching randomization of the entire D1 and/or D2 cohorts or minimal evaluable criteria as defined, a final safety SST will be held for Cohort D1 and/or D2 with all available PK data at the time of Part 1 termination.

Before escalating to the next higher dose level, there must be agreement that the current emerging safety, tolerability, and PK data support dose escalation. The appropriate quality control checks on the reviewed data and the conclusions of the SST will be documented in writing before allowing study progression.

Safety monitoring will continue after dose escalation, in accordance with the visit schedule, which encompasses approximately 12 additional weeks of follow-up.

5.3.2. Dosing (Part 2)

Dosing in Part 2 will begin at the Sponsor's discretion. Prior to start of dosing, the SST must review safety and PK data from Cohorts C1 and C2 (Part 1) and there must be agreement that the current emerging safety, tolerability, and PK data support the start of dosing in Part 2.

Participants who were assigned to Cohorts A, B, C1, and C2 and who have completed Week 25 (Day 175) Visit in Part 1 will receive BIIB105 at 60 mg in Part 2. Participants who were

assigned to Cohorts D1 and D2 and who have completed Week 25 (Day 176) Visit in Part 1 will receive BIIB105 at 120 mg in Part 2. The 60 mg dose may be increased, at the Sponsor's discretion, to doses up to 120 mg. Before increasing the dose level, the SST must review safety and PK data for Cohorts D1 and D2 (Part 1) as described in the Dose Escalation Plan and there must be agreement that the current emerging safety, tolerability, and PK data support the dose increase. Doses in Part 2 may also be decreased at the Sponsor's discretion at any time during the study.

Participants who were assigned to Cohorts A, B, C1, and C2 will have a ≥16-week washout period between the time of their last dose of study treatment in Part 1 and their first dose in Part 2. Therefore, they will have a 4-week unblinded Loading Dose Period, during which they will receive 3 doses of BIIB105 administered every 2 weeks (on Days 1, 15, and 29).

Participants who were assigned to Cohorts D1 and D2 will not have had a washout period between their last dose of study treatment in Part 1 and their first dose in Part 2. Therefore, they will have a 4-week blinded Loading Dose Period, to protect the blind in Part 1. During this blinded Loading Dose Period, participants who received BIIB105 during Part 1 will receive two doses of BIIB105, on Days 1 and 29, and placebo on Day 15. Participants who received placebo in Part 1 will receive three doses of BIIB105 administered every 2 weeks (on Days 1, 15, and 29). Participants from Cohorts D1 and D2 must not receive their first dose in Part 2 sooner than 4 weeks after their last dose in Part 1.

For all participants, the Loading Dose Period will be followed by an unblinded Maintenance Dose Period, where participants will receive maintenance doses of BIIB105 administered once every 4 weeks (up to approximately Week 156: either to Week 104, OR until the last participant enrolled has had the opportunity for their Part 2 Day 365 visit [Week 52], whichever occurs later). After the Maintenance Dose Period, participants will have an approximately 12-week follow-up period.

The SST will review safety and PK data from the extension cohorts at regular intervals.

5.4. Study and Cohort Stopping Rules

5.4.1. Cohort Suspension

If 1 participant experiences either an SAE or a medically unacceptable AE (as defined by the Investigator or the Sponsor), the Sponsor Medical Director and Global Medical Safety Physician will review relevant safety information and obtain more information from the Investigator, if necessary. If the AE is assessed as unrelated to study treatment by both the Investigator and the Sponsor (e.g., is a known sign or symptom of ALS or is a known effect of the LP procedure), dose suspension is not necessary.

If the SAE or medically unacceptable AE (as determined by the Investigator or the Sponsor) is assessed as related to study treatment by the Investigator or the Sponsor, then dosing at and above the dose level at which the event occurred will be suspended until the event has been fully evaluated by the SST. Depending on the nature, severity, suspected on- or off-target toxicity,

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outcome, and frequency of the event, a decision (documented with supporting rationale) will be made to proceed with one of the following:

- Request additional safety data.
- Continue dosing the remaining participants within the cohort.
- Randomize additional participants to the current cohort.
- Enroll additional participants to previous (lower dose) cohort.
- Proceed with the planned dose escalation in the next cohort.
- Dose a cohort with an intermediate lower dose.
- Stop the study.

The review will also include all available preliminary PK data from the current and preceding cohort(s).

If the study is suspended, dosing of the cohort cannot resume until both of the following have occurred:

- The Sponsor SST has completed the safety evaluation and the Investigator has received written approval from the Sponsor to resume dosing, and
- Where applicable, a rationale for the continuation of the study, including an amended protocol if required, is submitted to the relevant regulatory agency(ies) as a substantial amendment and subsequently approved before dosing can resume.

Following the SST review of safety and PK data for Cohort D1 (Part 1), if there is agreement that the current emerging safety, tolerability, and PK data support continued dosing at 120 mg, the abovementioned dose suspension rules will no longer apply. The Sponsor may still determine that a dose suspension is required at any time due to emerging safety data.

5.4.2. Dose Termination

After evaluation of safety, tolerability, and PK data by the SST, Investigator, and if required, any ad hoc members, further dosing at the current level and dose escalation will be terminated if any of the following is observed:

- Three similar SAEs (unless related to disease progression or unrelated to BIIIB105 upon medical review) are reported for participants receiving active study treatment within the same cohort.
- Four or more similar AEs are reported for participants receiving active study treatment (unless related to disease progression or unrelated to BIIIB105 upon

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medical review) that are either not tolerable (as reported by the participant) or deemed a medically unacceptable risk by the SST.

- Sponsor requests that dosing be terminated.

Following the SST review of safety and PK data for Cohort D1 (Part 1), if there is agreement that the current emerging safety, tolerability, and PK data support continued dosing at 120 mg, the abovementioned dose termination rules will no longer apply. The Sponsor may still determine that a dose termination is required at any time due to emerging safety data.

5.4.3. Study Termination

The Sponsor may terminate this study at any time after informing the Investigator, ethics committee, and applicable regulatory agencies. The Sponsor will notify Investigators when the study is to be placed on hold, completed, or terminated.

The study will be terminated if no dose is deemed to be safe.

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

- The discovery of an unexpected or serious risk to participants enrolled in the study.
- Dose termination for all ongoing cohorts and no agreement between the SST and Investigator to replace the planned dose of the current or subsequent cohorts with a lower dose.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

If, in light of emerging data, the Sponsor decides to continue testing, evaluation, or development of the product only for a specific subpopulation of ALS (for example, PolyQ-ALS), the study may be terminated for participants who do not meet criteria for the subpopulation.

5.5. Unscheduled Visits

Data collected during UVs should be recorded on the participant's CRFs only if the data support protocol objectives and/or are required for safety monitoring.

5.6. End of Study

5.6.1. End of Part 1

The end of Part 1 (placebo-controlled study) is last participant, last visit in Part 1. Final analyses of Part 1 will be performed after the last participant, last visit has been completed for Part 1, and the database for Part 1 has been locked.

5.6.2. End of Study

The end of study is last participant, last visit for final collection of data in Study 275AS101.

Following end of study, follow-up on vital status and date of death (if deceased) will be performed for participants who provide optional consent for data collection after study completion.

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6. STUDY POPULATION

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

For Investigator questions regarding participant eligibility or clinical significance of abnormalities, discussion with the study Medical Monitor is strongly encouraged.

6.1. Inclusion Criteria

6.1.1. Part 1

1. Ability of the participant to understand the purpose and risks of the study and indicate informed consent, and the ability of the participant or the participant's legally authorized representative, to provide signed and dated informed consent and authorization to use protected health information in accordance with national and local privacy regulations.

2. Aged 18 years or older at the time of informed consent or participant meets the minimum age of consent in accordance with national regulations (whichever is higher).

3. All women of childbearing potential and all men must ensure that highly effective contraception is used during the study and for at least [redacted] for female participants and [redacted] for male participants 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 [redacted] after their last dose of study treatment, while male participants should not donate sperm for the duration of the study and for at least [redacted] after their last dose of study treatment.

4. Participants in Cohorts A, B, C1, and D1, must meet the laboratory-supported probable, probable, or definite criteria for diagnosing ALS according to the World Federation of Neurology El Escorial criteria (revised according to the Airlie House Conference 1998 [Brooks 2000]). Participants in Cohorts C2 and D2 must meet any of the prior conditions but may also only meet clinically possible criteria for diagnosing ALS, or exhibit weakness attributable to ALS in the presence of ATXN2 intermediate repeats.

5. In participants in Cohorts C2 and D2, confirmed intermediate CAG/CAA repeat expansion in the *ATXN2* gene as defined by at least 1 allele carrying 30 to 33 CAG/CAA repeats.

6. No known presence or family history of mutations in the *SOD1* or *FUS* genes.

7. SVC criteria:

a. In participants in Cohorts A, B, C1, and D1, SVC $\geq$ 60% of predicted value as adjusted for sex, age, and height (from the sitting position).
b. In participants in Cohort C2 and D2, SVC $\geq$ 50% of predicted value as adjusted for sex, age, and height (from the sitting position).

8. If taking riluzole, participant must be on a stable dose for ≥ 30 days prior to Day 1 and expected to remain at that dose until the final study visit, unless the Investigator determines that it should be discontinued for medical reasons, in which case it may not be restarted during the study.

9. Participants taking concomitant edaravone at study entry must be on a stable dose for ≥ 60 days prior to the first dose of study treatment (Day 1). Participants taking concomitant edaravone must be willing to 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 of this study.

10. Screening values of coagulation parameters including platelet count, INR, PT, and APTT should be within normal ranges. Coagulation tests done at a local laboratory may be used for screening purposes, in order to reduce participant burden. Coagulation tests may be repeated once at the local laboratory if, in the opinion of the Investigator, values of the initial tests are out of range but 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 and after a consultation with the Sponsor.

11. Has an informant/caregiver who, in the Investigator's judgment, has frequent and sufficient contact with the participant as to be able to provide accurate information about the participant's cognitive and functional abilities at Screening. An informant/caregiver should be available at Screening. The participation of the same informant/caregiver for the duration of the study is encouraged.

6.1.2. Part 2

1. Ability of the participant to understand the purpose and risks of the study and indicate informed consent, and the ability of the participant or the participant's legally authorized representative to provide signed and dated informed consent and authorization to use protected health information in accordance with national and local privacy regulations.

2. Participants must have completed Study 275AS101 Part 1 through Week 25 (Day 175 Visit for Cohorts A, B, C1, C2; Day 176 Visit for Cohorts D1, D2). This inclusion criterion does not apply to a participant if Part 1 was terminated by the Sponsor before the participant reached Week 25.

3. Participants from Cohorts A, B, C1, and C2 must have a washout of ≥16 weeks between the last dose of study treatment received in Study 275AS101 Part 1 and the first dose of BIIB105 received in Study 275AS101 Part 2. Participants from Cohorts D1 and D2 do not require a washout period.

4. All women of childbearing potential and all men must ensure that highly effective contraception is used during the study and for at least [redacted] for female participants and [redacted] for male participants 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 [redacted] after their last dose of study treatment, while male participants should not donate sperm for the duration of the study and for at least [redacted] after their last dose of study treatment.

5. If taking riluzole, participant must be on a stable dose for ≥ 30 days prior to Day 1 and expected to remain at that dose until the final study visit, unless the Investigator determines that it should be discontinued for medical reasons, in which case it may not be restarted during the study.

6. Participants taking concomitant edaravone at study entry must be on a stable dose for ≥ 60 days prior to the first dose of study treatment (Day 1). Participants taking concomitant edaravone must be willing to 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 of this study.

7. Screening values of coagulation parameters including platelet count, INR, PT, and APTT should be within normal ranges. Coagulation tests done at a local laboratory may be used for screening purposes, in order to reduce participant burden. Coagulation tests may be repeated once at the local laboratory if, in the opinion of the Investigator, values of the initial tests are out of range but 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 and after a consultation with the Sponsor.

6.2. Exclusion Criteria

6.2.1. Part 1

Medical History and Current Health Status

1. History or positive test result at Screening for HIV. The requirement for testing at Screening may be omitted if it is not permitted by local regulations.

2. Current hepatitis C infection (defined as positive HCV antibody and detectable HCV RNA). Participants with positive HCV antibody and undetectable *HCV* RNA are eligible to participate in the study.

3. Current hepatitis B infection (defined as positive for HbsAg and/or total anti-HBc). Participants with immunity to hepatitis B from previous natural infection (defined as negative HbsAg, positive anti-HBc, and positive anti-HBs) or vaccination (defined as negative HbsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.

4. History of alcohol or substance abuse ≤ 6 months of Screening that would limit participation in the study, as determined by the Investigator.

5. Current or anticipated need, in the opinion of the Investigator, of a diaphragm pacing system during the study period.

6. Presence of tracheostomy.

7. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening Period.

8. History of a deep venous thrombosis or pulmonary embolism ≤ 2 years of Screening, or since the date of ALS diagnosis, whichever is longer.

9. In participants from Cohorts A, B, C1, and D1, history of myocardial infarction, as determined by the Investigator.

10. In participants from Cohorts A, B, C1, and D1, poorly controlled type 1 or 2 diabetes mellitus defined as HbA1c ≥ 8% during Screening.

11. Ongoing medical condition (e.g., wasting or cachexia, severe anemia) that would, in the opinion of the Investigator, interfere with the conduct or assessments of the study.

12. Significant cognitive impairment, clinical dementia, or unstable psychiatric illness, including psychosis, suicidal ideation, suicide attempt, or untreated major depression ≤ 90 days of Screening that in the opinion of the Investigator would interfere with the study procedures.

13. History of allergies to anesthetics that will be used for the LP procedure per institutional practice.

14. 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 intraoperative or postoperative bleeding. These 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).

15. Presence or anticipated need of an implanted shunt for the drainage of CSF or an implanted CNS catheter at any time during the study.

16. Presence or anticipated need of an implanted intravenous port/catheter at any time during Part 1 of the study.

17. Clinically significant abnormalities in hematology or blood chemistry parameters, as determined by the Investigator that would render the participant unsuitable for enrollment.

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18. Clinically significant, as determined by the Investigator, 12-lead ECG abnormalities, including corrected QT interval using Fridericia's correction method of > 450 msec for males and > 460 msec for females.

19. In participants in Cohorts A, B, and C1, prescreening ALSFRS-R slope > ***-0.4*** points/month, where prescreening ALSFRS-R slope is defined as: (ALSFRS-R score at Screening - 48) / (months from date of symptom onset to date of Screening). This criterion is not applicable for Cohorts C2, D1, and D2.

Medications

20. Treatment with another investigational drug (including investigational drugs for ALS through compassionate use programs) or biological agent within 1 month or 5 half-lives of study agent, whichever is longer, before Screening.

21. Treatment with an approved disease-modifying therapy for ALS other than riluzole or edaravone within 1 month or 5 half-lives of therapy, whichever is longer, before completion of Screening.

22. Treatment with an antiplatelet or anticoagulant therapy that cannot safely be interrupted for LP according to local standard of care and/or institutional guidelines, in the opinion of the Investigator or Prescriber.

Other

23. Female participants who are pregnant or currently breastfeeding and those intending to become pregnant during the study.

24. Current enrollment or a plan to enroll in any interventional clinical study. Participation in a noninterventional study focused on ALS natural history may be allowed at the discretion of the Investigator and after consultation with the Sponsor.

25. Inability to comply with study requirements.

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

6.2.2. Part 2

Medical History and Current Health Status

1. History or positive test result at Screening for HIV. The requirement for testing at Screening may be omitted if it is not permitted by local regulations. If participants from Cohorts D1 and D2 who would seamlessly roll from Part 1 into Part 2 test positive for HIV during screening for Part 2 but are clinically asymptomatic, they may enroll in Part 2 at the discretion of the Investigator.

2. Current hepatitis C infection (defined as positive HCV antibody and detectable HCV RNA). Participants with positive HCV antibody and undetectable *HCV* RNA are eligible to participate in the study. If participants from Cohorts D1 and D2 who would seamlessly roll from Part 1 into Part 2 test positive for hepatitis C during screening for Part 2 but are clinically asymptomatic, they may enroll in Part 2 at the discretion of the Investigator.

3. Current hepatitis B infection (defined as positive for HbsAg and/or total anti-HBc). Participants with immunity to hepatitis B from previous natural infection (defined as negative HbsAg, positive anti-HBc, and positive anti-HBs) or vaccination (defined as negative HbsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study. If participants from Cohorts D1 and D2 who would seamlessly roll from Part 1 into Part 2 test positive for hepatitis B during screening for Part 2 but are clinically asymptomatic, they may enroll in Part 2 at the discretion of the Investigator.

4. History of alcohol or substance abuse ≤ 6 months of Screening that would limit participation in the study, as determined by the Investigator.

5. Current or anticipated need, in the opinion of the Investigator, of a diaphragm pacing system during the study period.

6. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening Period that, according to the Investigator, would interfere with the conduct or assessments of the study.

7. In participants from Cohorts A, B, C1, and D1, history of myocardial infarction, as determined by the Investigator.

8. In participants from Cohorts A, B, C1, and D1, poorly controlled type 1 or 2 diabetes mellitus defined as HbA1c ≥ 8% during Screening.

9. Ongoing medical condition (e.g., wasting or cachexia, severe anemia) that would, in the opinion of the Investigator, interfere with the conduct or assessments of the study.

10. Significant cognitive impairment, clinical dementia, or unstable psychiatric illness, including psychosis, suicidal ideation, suicide attempt, or untreated major depression ≤ 90 days of Screening that in the opinion of the Investigator would interfere with the study procedures.

11. History of allergies to anesthetics that will be used for the LP procedure per institutional practice.

12. 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 intraoperative or postoperative bleeding. These 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).

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13. Presence or anticipated need of an implanted shunt for the drainage of CSF or an implanted CNS catheter at any time during the study.

14. Clinically significant abnormalities in hematology or blood chemistry parameters, as determined by the Investigator that would render the participant unsuitable for enrollment.

15. Clinically significant, as determined by the Investigator, 12-lead ECG abnormalities, including corrected QT interval using Fridericia's correction method of > 450 msec for males and > 460 msec for females.

Medications

16. Treatment with another investigational drug (including investigational drugs for ALS through compassionate use programs; excluding BIIB105) or biological agent within 1 month or 5 half-lives of study agent, whichever is longer, before Screening.

17. Treatment with an antiplatelet or anticoagulant therapy that cannot safely be interrupted for LP according to local standard of care and/or institutional guidelines, in the opinion of the Investigator or Prescriber.

Other

18. Female participants who are pregnant or currently breastfeeding and those intending to become pregnant during the study.

19. Current enrollment or a plan to enroll in any interventional clinical study. Participation in a noninterventional study focused on ALS natural history may be allowed at the discretion of the Investigator and after consultation with the Sponsor.

20. Inability to comply with study requirements.

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

6.3. Screening, Retesting, and Screen Failures

6.3.1. Screening

Once informed consent is obtained, screening assessments can occur. At this time, a unique identification number is assigned that will be used on study-related documents pertaining to the participant. Any identification numbers that are assigned will not be reused even if the participant does not receive treatment or continue in the study. Study sites are required to document all screened participants initially considered for inclusion in the study.

A participant or their legally authorized representative must provide written informed consent before any screening tests are performed. A participant's informants/caregivers must also

provide written informed consent to participate in the study prior to providing any information on either themselves and/or participants. It is preferable that the same informant/caregiver participates and completes the informant/caregiver assessments for the duration of the study.

The Screening Period may be extended up to a total duration of 42 days for eligible individuals who cannot complete the Day 1 Visit within 28 days of signing the ICF.

Part 2 Screening:

For consented participants from Cohorts D1 and D2, the Screening Period for Part 2 begins at the Part 1 Day 169 Visit. Results from Day 169 visit and Day 176 visits may be used for the purpose of screening and do not need to be repeated as long as they are conducted within 1-month of Baseline/loading dose visit (Part 2 Day 1).

For Cohorts A, B, C1 and C2, the Screening Period may be extended up to a total duration of 42 days for eligible individuals who cannot complete the Day 1 Visit within 28 days of signing the ICF (Screening assessments may be performed over multiple days to reduce participant burden.

6.3.2. Retesting

Participants who have a nonclinically significant out-of-range laboratory result can be retested 1 time only at the discretion of the Investigator after discussion with the Sponsor. The Screening Period may be extended up to a total duration of 42 days for eligible individuals who require retesting of laboratory results, including genetic testing results. Individuals who signed the ICF and subsequently do not meet concomitant medication criteria can have their Screening Period extended up to 42 days to ensure that the requirements for concomitant medication stabilization have been met.

The results of the most recent (i.e., obtained at a previous visit) centrally read coagulation tests and platelet count must be reviewed before each LP can be performed. Should the results suggest, in the opinion of the Investigator, that an LP may be safely performed, then no further laboratory values need to be reviewed. However, should, in the opinion of the Investigator, repeat coagulation and platelet tests be clinically indicated, then these tests may be repeated locally to facilitate timely review. Results of any repeat tests must be available before the LP can be performed.

6.3.3. Screen Failures

Screen failures are defined as participants who sign the ICF but are not subsequently randomized. If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant's source documents and on the screening log. Participants who fail screening may be permitted to be rescreened once at the Investigator's discretion after discussion with the Sponsor. All screening assessments would need to be repeated during rescreening except for the following:

- FSH level in female participants with postmenopausal state confirmed by level obtained in previous screening for this study.

- For participants in Cohorts C2 or D2, confirmation of intermediate (30 to 33) CAG/CAA repeats in at least 1 allele in the ATXN2 gene by the central laboratory, if available from previous screening for this study.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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7. STUDY TREATMENT

7.1. Regimen

In Part 1:

Each participant will receive an IT injection of study treatment (BIIB105 or placebo) over approximately 1 to 3 minutes every 14 days (i.e., Days 1, 15, and 29 in Part 1) during the loading period and every 28 days thereafter up to Day 85 (for Cohorts A, B, C1, and C2) or Day 169 (for Cohorts D1 and D2). Doses of BIIB105 will range from 5 mg up to 120 mg, all formulated in a final volume of [redacted] mL. Prior to injection, approximately [redacted] mL of CSF will be collected for analyses. Depending on institutional guidelines, anesthesia or sedation may be used for the LP procedure. Refer to and follow the DHA.

The dosage cannot be modified.

In Part 2:

Participants from Cohorts A, B, C1, and C2 will have a ≥16-week washout period. Participants will receive an IT injection of 60 mg BIIB105 [redacted] every 14 days (i.e., Part 2 Days 1, 15, and 29) during the unblinded loading period, and every 28 days thereafter up to either Day 729 (Week 104), or until the last participant enrolled has had the opportunity for their Part 2 Day 365 visit (Week 52), whichever occurs later. The 60 mg dose may be increased, at the Sponsor's discretion, to doses up to 120 mg. Before increasing the dose level, the SST must review safety and PK data for Cohort D1 (Part 1) and there must be agreement that the current emerging safety, tolerability, and PK data support the dose increase.

Participants from Cohorts D1 and D2 will not have a washout period and will have a blinded Loading Dose period. Participants who received placebo in Part 1 will receive 3 loading doses of BIIB105 120 mg approximately once every 2 weeks (Days 1, 15, and 29), while participants who received BIIB105 in Part 1 will receive 2 doses of BIIB105 120 mg, on Days 1 and 29, and placebo on Day 15. After the blinded Loading Dose Period, participants from Cohorts D1 and D2 will receive BIIB105 120 mg at each unblinded Maintenance Dose Visit thereafter (either up to Week 104, or until the last participant enrolled has had the opportunity for their Part 2 Day 365 visit [Week 52], whichever occurs later). For participants from Cohort D1 and D2, the first dose for each participant in Part 2 will not occur less than 4 weeks after their last dose in Part 1.

Doses in Part 2 for participants from all cohorts may be decreased at any time in the study at the Sponsor's discretion.

Doses of BIIB105 in Study 275AS101 Part 2 will all be formulated in a final volume of [redacted] mL. Prior to injection, approximately [redacted] mL of CSF will be collected for analyses. Depending on institutional guidelines, anesthesia or sedation may be used for the LP procedure. Refer to and follow the DHA.

The dosage cannot be modified.

7.2. Study Treatment Management

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

Site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

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.

7.3. Study Treatment

7.3.1. BIIB105

BIIB105 is supplied as a sterile, buffered, and isotonic solution in single-use clear vials containing study treatment either at a concentration of [redacted] mg/mL and a targeted volume of [redacted] mL per vial to ensure maximum withdrawal of [redacted] mL for dose preparation, or at a concentration of [redacted] mg/mL with a targeted volume of [redacted] mL per vial to ensure maximum withdrawal of [redacted] mL for dose preparation (once this presentation is available for use at clinical study sites). This is accompanied by aCSF to be used as diluent where needed. Both BIIB105 and aCSF vials are sealed with a butyl rubber stopper and aluminum over seal with flip-off cap.

The contents of the BIIB105 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.

7.3.1.1. Preparation

The individual preparing BIIB105 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 BIIB105, do not use the study treatment. The vial(s) in question should be saved at the study site and the problem immediately reported to the Sponsor.

Contact information for reporting a problem is provided in the study reference guide.

7.3.1.2. Storage

Study treatment must be stored in a secure location.

BIIB105 is to be stored at 2°C to 8°C (36°F to 46°F), in a monitored, locked refrigerator with limited access and protected from light. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

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7.3.1.3. Handling and Disposal

The Investigator must return all used and unused vials of BIIB105 as instructed by the Sponsor unless approved for onsite destruction.

If any BIIB105 supplies are to be destroyed at the study site, the institution or appropriate site staff 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.

7.3.1.4. 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, all vials both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made between the amount of BIIB105 supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation must be provided for any discrepancies.

7.3.2. Placebo

Sponsor provided matching placebo is supplied as a sterile, buffered, and isotonic solution in vials. The drug supply label will include conditions for storage, lot number, and other pertinent information.

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

7.4. Blinding Procedures

The Investigator, study staff (except for designated pharmacy staff), and participants will be blinded to the randomized treatment assignments. To maintain the study blind, it is imperative that participant treatment assignments are not shared with the participants, their families, or any member of the blinded study team, both at the site and at the Sponsor and CRO, except the unblinded designated Study Pharmacy Staff and designated Sponsor personnel.

The SST, Biostatistician, Clinical Pharmacologist, and, if required, any ad hoc members, may be unblinded in order to review all safety and available PK data, to assess safety and tolerability, and to make informed decisions regarding dose escalation Section 5.3 and/or for interim analyses of the data.

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At the end of the study (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, the Sponsor will provide the randomization codes to Investigators, who then can inform their participants about the treatment received.

In the event of a medical emergency that requires unblinding of a participant's treatment assignment, refer to Section 12.4.3.1.

7.5. Precautions

Depending on institutional guidelines, anesthesia or sedation may be used for the LP procedure. On dosing days in Part 1, (except Dose 1), participants will remain at the study site for at least 6 hours postdose for safety monitoring. In Part 2, participants who receive the 60 mg dose will remain at the study site for at least one hour postdose, and participants who receive the 120 mg dose will remain at the study site for at least 2 hours postdose for safety monitoring. Participants can be discharged at the discretion of the Investigator and in compliance with the institutional requirements, once the participant has adequately recovered from the dosing procedure. Participants will receive a safety follow-up TC approximately 24 hours after the procedure. During the Follow-up Period, participants will remain under observation in the clinic for approximately 1 hour after the LP procedure and will receive a safety follow-up TC approximately 24 hours after the procedure. Refer to and follow the DHA.

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

7.6. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

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

7.7. Concomitant Therapy and Procedures

7.7.1. Concomitant Therapy

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

Participants should be instructed to contact their Investigators before taking any new medications, including nonprescription drugs and herbal preparations. Use of concomitant medication for symptom management during the study is at the discretion of the Investigator.

7.7.1.1. 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) and should remain on this stable dose of riluzole until the Final/ET Visit, unless riluzole use must be discontinued in the judgment of

the Investigator, in which case it should not be restarted during the study. If participants are not receiving riluzole at Part 1 Day 1, they should not initiate it in Part 1.

Participants taking concomitant edaravone at study entry must be receiving a stable dose for ≥ 60 days (2 treatment cycles) prior to the first dose of study treatment (Day 1) and should remain on this stable dose of edaravone until the Final/ET Visit, unless edaravone use must be discontinued in the judgment of the Investigator, in which case it should not be restarted during the study. If participants are not receiving edaravone at Part 1 Day 1, they should not initiate it in Part 1. Edaravone may not be administered on dosing days of this study.

Daily intake of all concomitant medication, vitamins, and supplements should be stabilized at least 14 days prior to Day 1. Doses of vitamins, minerals, and supplements greater than the recommended daily dose should be discouraged during the study.

Supplements that are subject to dose limits from at least 14 days prior to Day 1 and that should remain stable throughout the study are as follows: creatine 5 g/day and vitamin E 1000 IU/day. These daily limits include the total doses obtained through the combination use of daily multivitamins and supplements.

7.7.1.2. Disallowed Concomitant Therapy

Treatment with an antiplatelet or anticoagulant therapy that cannot safely be interrupted for LP according to local standard of care and/or institutional guidelines, in the opinion of the Investigator or Prescriber, should not be taken.

Use of a diaphragm pacing system, investigational drugs other than the investigational product (including drugs for ALS through compassionate use programs), or ASOs is prohibited for the duration of the study.

Use of indwelling injection ports/catheters are prohibited during Part 1 of the study.

Use of approved disease-modifying treatments for ALS other than riluzole or edaravone (i.e., sodium phenylbutyrate and taurursodiol in applicable geographies) is prohibited during Part 1 of the study.

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.

7.7.2. 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 Day 1 and the Final/ET Visit.

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7.8. Continuation of Treatment

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

8. RULES FOR DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL FROM STUDY FOR INDIVIDUAL PARTICPANTS

8.1. Discontinuation of Study Treatment

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

- The participant becomes pregnant. Report the pregnancy according to the instructions in Section 12.4.1.
- The participant withdraws consent to continue study treatment.
- The participant experiences an AE that necessitates permanent discontinuation of study treatment.
- The participant experiences a medical emergency that necessitates unblinding of the participant's treatment assignment.
- The participant is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Sponsor.

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

If a participant received a dose of study treatment, then he or she will be encouraged to complete all the scheduled safety evaluations during the ET Visit.

Participants who discontinue treatment are encouraged to remain in the study and continue protocol-required tests and assessments, where possible.

8.2. Lost to Follow-Up

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

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

- The site must attempt to contact the participant, reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit

schedule, and ascertain whether the participant wishes to and/or should continue in the study.

- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, that participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.3. Withdrawal of Participants From the Study

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

- The participant withdraws consent for participation in the study.

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

Participants who withdraw from the study prior to completing study follow-up (last visit) in Part 1 may be replaced at the same dose cohort, at the discretion of the Sponsor.

After withdrawal from the study, follow-up on vital status and date of death (if deceased) will be performed for participants who provide optional consent for data collection after study withdrawal.

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9. SAFETY ASSESSMENTS

See Section 1 for the timing of all safety assessments.

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

9.1. Clinical Assessments

The following clinical assessments will be performed to evaluate the safety profile of BIIB105:

- AE and SAE recording.
- Physical examinations.
- Neurological examinations (to be assessed by a trained specialist): Cranial nerves, motor, reflexes, cerebellar function, and mental status (MMSE in Part 1). A detailed list will be provided in the Study Reference Manual.
- Vital sign measurements: Temperature, heart rate, systolic and diastolic blood pressure, and respiratory rate will be measured after the participant has rested for at least 5 minutes.
- Weight and height measurements.
- 12-Lead ECGs: ECGs are to be done in triplicate in the supine position (or semi-recumbent position, if supine is not possible).
- C-SSRS:
  - In Part 1, the “Since Last Visit” version of C-SSRS will be used from Day 8 onward.
  - In Part 2, participants from Cohorts D1 and D2 will use "Since Last Visit" version of C-SSRS on Day 1 onward. Participants from Cohorts A, B, C1, and C2 will use the “Since Last Visit” version of the C-SSRS from Day 15 onward.
- Concomitant therapy and procedure recording.

9.2. Laboratory Assessments

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

The following laboratory assessments will be performed to evaluate the safety profile of BIIB105:

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- Hematology: Complete blood count with differential
- Coagulation: INR, PT, and APTT
- Blood chemistry: Total protein, albumin, HbA1c, lipid panel, 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)
- Urine and/or serum pregnancy tests
- CSF analysis: Red blood cell count, white blood cell count, protein, and glucose

9.3. Product-Specific Safety Assessments

Anti-BIIB105 antibody assessments will be conducted when indicated.

10. PHARMACOKINETIC ASSESSMENTS

BIIB105 concentrations in the serum and CSF will be determined using validated assays.

Samples for analysis of BIIB105 concentrations in serum and CSF will be collected from each participant at timepoints specified in Table 1 and Table 2.

See Section 1 for the timing of all assessments.

The following PK parameters will be assessed, when feasible, to assess the PK of BIIB105:

- AUC_{inf}
- AUC_{last}
- C_{max}
- T_{max}
- $t_{½}$

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

11. PHARMACODYNAMIC AND EFFICACY ASSESSMENTS

See Section 1 for the timing of all assessments.

11.1. Pharmacodynamic Assessments

[redacted], plasma, [redacted] will be collected to assess the modulation of potential PD biomarkers that may be related to BIIB105 activity or ALS disease progression. The assessments may include, but are not limited to, [redacted]. The biomarkers to be analyzed may include, but are not limited to, ATXN2, NfL, [redacted]

[redacted]

11.2. Assessments of Clinical Function and Survival

The following [redacted] assessments will be performed to evaluate the effects of BIIB105 on clinical function and survival:

- SVC
- ALSFRS-R (standard)
- [redacted]
- [redacted]
- [redacted]
- HHD
- [redacted]
- [redacted]
- [redacted]
- Ventilation diary
- Collection of vital status before and after study withdrawal or completion

11.2.1. Slow Vital Capacity

Vital capacity will be measured by means of an SVC test, collected by certified assessors according to a standardized protocol established by the Northeast ALS Consortium.

11.2.2. ALS Functional Rating Scale-Revised (standard)

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 Part 1, this study site staff member will remain blinded to participants' treatment assignments and to the results of other assessments. In Part 2, this study site staff member will remain blinded to participants' treatment assignments and to the results of other assessments during the blinded loading dose period for participants in Cohorts D1 and D2.

11.2.6. Handheld Dynamometry

Muscle strength is an important determinant of both function and ultimate survival in ALS. Quantitative muscle strength will be evaluated using HHD, which tests isometric strength of multiple muscles using standard participant positioning [Shefner 2016]. Approximately 8 muscle groups will be examined (per each side) in both upper and lower extremities.

[redacted]

11.2.10. Participant Ventilation Diary

Participants will be given diaries to record use of ventilation. This diary will be reviewed with study site staff at each visit. Refer to the Study Reference Guide for details.

11.2.11. Collection of Vital Status Before and After Study Withdrawal or Completion

Participants' vital status will be collected throughout the study. For participants who provide optional consent for data collection after study withdrawal or completion, follow-up on vital status and date of death (if deceased) will be performed.

11.3. Pharmacogenetic and Genetic Assessments

Genetic polymorphism impacting genes encoding drug targets or the downstream pathways, as well as proteins that impact drug absorption, distribution, metabolism, and elimination, may affect the safety and efficacy of the study treatment.

A DNA sample will be collected for genomic analysis. This is a one-time blood collection required at Screening for all participants, as outlined in Table 1 and Table 2 . For all cohorts, this collection is governed by the main ICF for the study.

Approximately 10% of patients diagnosed with ALS are 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 the *ATXN2* intermediate polyCAG repeat mutation. The DNA sample will be used to determine the presence or absence of an *ATXN2* intermediate polyCAG repeat mutation. The DNA sample may also be analyzed for genetic variation in the *ATXN2* gene to determine the spectrum of likely pathogenic mutations in the gene and to assess if *ATXN2* polymorphisms affect response to treatment. In addition, these samples 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, FUS, chromosome 9 open reading frame 72, optineurin, valosin-containing protein, ubiquilin 2, profilin 1*, and *SOD1*.

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

In the future, as the understanding of ALS and BIIB105 increases, additional genetic analyses may be warranted to refine the knowledge of the molecular basis of the disease and the drug response and to advance the development of novel therapeutics. This sample will only be used in genetic analyses to understand ALS, neurodegeneration, and the response to BIIB105.

The DNA samples will be coded with the participant's identification number and may be stored for 15 years or a duration dictated by local, national, or regional laws or regulations. No genotyping or genetic data will be provided to the participant. Participants may withdraw consent and request to have their sample destroyed at any time and no further genetic data will be generated; any data already generated will not be destroyed.

In addition, where allowed by local, regional, and national regulatory authorities and ethics committees, participants will be offered the option for [redacted] that may be used to understand the biology of ALS and other diseases and traits of interest to the Sponsor and/or to develop diagnostic and

analytical tests. Participants who opt for samples to be retained for future unspecified use will be required to sign a separate ICF.

[redacted]

12. 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 and/or his/her legally authorized representative and/or main informant/caregiver must be given the names and telephone numbers of site staff for reporting AEs and medical emergencies. Throughout the protocol, the Sponsor is named, but reporting may be done through a CRO.

12.1. Definitions

12.1.1. 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 assessment (e.g., laboratory value, vital sign, and ECG) result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

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

12.1.2. 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.

A medically important event is an AE 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.)

12.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the 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 12.1.2 is met.

12.2. Safety Classifications

12.2.1. 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 12.1.2.
- The relationship of the event to study treatment or LP as defined in Section 12.2.2.
- The severity of the event as defined in Section 12.2.3.

12.2.2. Relationship of Events to Study Treatment or Lumbar Puncture

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

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

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 AE, 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 AE, 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.

12.2.3. 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 (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)
2	Moderate AE (minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living)
3	Severe or medically significant AE (not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living)
4	Life-threatening AE (urgent intervention indicated)
5	Death related to AE

12.2.4. Expectedness of Events

Expectedness of all AEs will be determined by the Sponsor according to the Investigator's Brochure for BIIB105.

12.3. Monitoring and Recording Events

12.3.1. Adverse Events

Any AE experienced by the participant between the time of first dose of study treatment and the Final/ET 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, 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 up by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will be recorded on the CRF, as applicable.

12.3.2. Serious Adverse Events

Any SAE experienced by the participant between the time of the signing of the ICF and the Final/ET Visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment and must be reported to the Sponsor within 24 hours as described in Section 12.3.3. Follow-up information regarding an SAE also must be reported within 24 hours.

Participants will be followed up 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 up by the Investigator until the event has resolved, stabilized, or returned to baseline status.

12.3.3. 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 site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

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

12.3.3.1. 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. 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.

12.3.4. 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.

12.4. Procedures for Handling Special Situations

12.4.1. Pregnancy

Female participants should not become pregnant during the study and for at least [redacted] after their last dose of study treatment, while male participants should not impregnate their partners during the study and for at least [redacted] 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 from first dose of study drug to [redacted] after their last dose of study treatment by faxing or emailing the appropriate form to the Sponsor within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete contact information. The Investigator or 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 or within [redacted] from their last dose of study treatment for females and [redacted] from their last dose of study treatment for males.

12.4.2. 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 or emailed to the Sponsor. All study treatment-related dosing information must be recorded on the dosing CRF.

12.4.3. Medical Emergency

In a medical emergency requiring immediate attention, 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.

12.4.3.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the participant's treatment assignment may influence the participant's clinical care, the Investigator may access the participant's 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 treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator can contact the Sponsor or designee to discuss such situations.

12.5. Contraception Requirements

All women of childbearing potential and all men must ensure that highly effective contraception is used during the study and for at least [redacted] for female participants and [redacted] for male participants 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 [redacted] after their last dose of study treatment, while male participants should not donate sperm for the duration of the study and for at least [redacted] after their last dose of study treatment.

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following conditions:

1. Postmenopausal

1.1. 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum FSH level > 40 mIU/mL

1.2. 6 weeks after surgical bilateral oophorectomy with or without hysterectomy

2. Posthysterectomy

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

For females:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected, or implanted progestogen-only hormonal methods of contraception associated with the inhibition of ovulation.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Bilateral tubal occlusion.

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- Female surgical sterilization (e.g., bilateral tubal ligation).
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

For males:

- Vasectomy with negative semen analysis at follow-up. If documentation is not available, the participant must use contraception.
- Sex only with a woman who uses the methods described for females if she is of childbearing potential.

True abstinence, when this is consistent with the preferred and usual lifestyle of the 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 study. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 12.4.1.

12.6. Safety Responsibilities

12.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the CRF 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 in female participants and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and fax or email it to the Sponsor within 24 hours of the site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the Sponsor within 24 hours of the site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the participants' medical records.

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- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the CRF, as applicable.

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

12.6.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before a site can enroll any participants, the Clinical Monitor is responsible for reviewing with 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.

13. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 4.

13.1. General Considerations

In general, for continuous data, summary statistics will be presented (e.g., mean, standard deviation, median, first and third quartile, and range). For categorical data, frequency counts and percentages will be presented. Demographic and baseline data will be summarized.

Analyses will be performed on data from Part 1 alone, data from Part 2 alone, and on integrated data from Part 1 and Part 2.

Placebo data in Part 1 may be pooled across cohorts for analyses. The Pooled Placebo 1 population is defined as participants from Cohorts A, B, C1, and D1 who received placebo in Part 1. The Pooled Placebo 2 population is defined as participants from Cohorts C2 and D2 who received placebo in Part 1.

13.2. Analysis Populations

13.2.1. Part 1

The Part 1 FAS population is defined as all randomized participants who received at least 1 dose of study treatment in Part 1. In analyses performed on the FAS, participants will be analyzed, based on the intent-to-treat (ITT) principle, according to their randomized treatment assignment regardless of treatment received.

The Part 1 safety analysis population is defined as all randomized participants who received at least 1 dose of study treatment in Part 1.

The Part 1 PK analysis population is defined as all randomized participants who received at least 1 dose of study treatment and have at least 1 postdose serum and/or CSF BIIB105 measurement in Part 1.

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

The Part 1 clinical function population is defined as the subset of the FAS population who have at least 1 postdose measurement in Part 1.

13.2.2. Part 2

The Part 2 FAS population is defined as all enrolled participants who received at least 1 dose of study treatment in Part 2.

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The Part 2 safety analysis population is defined as all participants who received at least 1 dose of study treatment in Part 2

13.2.3. Integrated Part 1 and Part 2

Integrated data for Part 1 and Part 2 will be analyzed based on the following populations defined for Part 1, with the exception of the safety data, which will be defined separately: Part 1 FAS population, Part 1 PK population, Part 1 PD population, and Part 1 clinical function population.

The Integrated Part 1 and Part 2 safety analysis population is defined as all randomized participants who received at least 1 dose of BIIB105 either in Part 1 or Part 2.

13.3. Methods of Analysis

13.3.1. Safety

For analyses of Part 1, safety data will be summarized by dose level and treatment assignment in Part 1 (BIIB105 5 mg [Cohort A], 20 mg [Cohort B], 60 mg [Cohorts C1+ C2], 120 mg [Cohorts D1+D2], Pooled Placebo 1+2), as well as by cohort and treatment assignment in Part 1 (BIIB105-treated Cohorts A, B, C1, C2, D1, and D2; Pooled Placebo 1 and Pooled Placebo 2).

For analyses of Part 2, safety data will be summarized by dose level in Part 2 (BIIB105 60 mg vs BIIB105 120 mg). [redacted]

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, safety data from the BIIB105-treated periods in Part 1 and Part 2 will be summarized, with baseline defined as the first dose of 120 mg BIIB105, regardless of whether the participant started this dose in Part 1 or Part 2. [redacted]

To assess the overall safety profile of 60 mg BIIB105, integrated Part 1 and 2 safety data may be presented for any participant who received at least one dose of 60 mg BIIB105, with baseline defined as first dose of 60 mg BIIB105. To assess the overall safety profile of 120mg BIIB105, integrated Part 1 and 2 safety data may be presented for any participant who received at least one dose of 120 mg BIIB105, with baseline defined as the first dose of 120 mg BIIB105.

13.3.1.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent AEs, SAEs, deaths, and AEs leading to treatment discontinuation, at minimum, will be summarized by system organ class and preferred term. The AEs level of severity and relationship to study treatment will also be similarly summarized. For the summary of AEs by severity, if a subject 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. Due to the different durations of exposure to

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BIIB105 and washout periods for some participants, exposure-adjusted incidence rates will also be summarized.

13.3.1.2. Laboratory Results

Laboratory data includes hematology, coagulation, blood chemistry, CSF assessments, and urinalysis, and will be summarized. Summary statistics for actual values and changes from baseline will be presented for quantitative laboratory data. In addition, shift tables will be used to tabulate the shifts from baseline to high/low status for each laboratory test.

13.3.1.3. Vital Signs

Incidence of clinically relevant abnormalities and changes from baseline in vital signs will be summarized using descriptive statistics.

13.3.1.4. C-SSRS

C-SSRS data will be listed for individual participants and summarized using frequency tables.

13.3.1.5. Electrocardiogram

Incidence of clinically relevant abnormalities and changes from baseline in ECGs will be summarized using frequency tables and descriptive statistics.

13.3.2. Pharmacokinetics

Serum and CSF BIIB105 concentrations will be summarized using descriptive statistics and, where warranted, plotted graphically over time both on linear and logarithmic scales. For Part 1, summaries of BIIB105 PK parameters will also be summarized using descriptive statistics.

For analyses of Part 1, PK data will be summarized by dose level in Part 1 (BIIB105-treated 5 mg [Cohort A], 20 mg [Cohort B], 60 mg [Cohorts C1 + C2], and 120 mg [Cohorts D1 + D2]).

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, PK data from the BIIB105-treated periods in Part 1 and Part 2 will be summarized, with baseline defined as the first dose of 120 mg BIIB105, regardless of whether the participant started this dose in Part 1 or Part 2.

[redacted]

To assess the overall PK profile of 60 mg BIIB105, integrated Part 1 and 2 PK data may be presented for any participant who received at least one dose of 60 mg BIIB105, with baseline defined as first dose of 60 mg BIIB105. To assess the overall PK profile of 120mg BIIB105, integrated Part 1 and 2 PK data may be presented for any participant who received at least one dose of 120 mg BIIB105, with baseline defined as the first dose of 120 mg BIIB105.

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[redacted]

13.3.4. Clinical Function and Quality of Life Measures

The actual scores and changes from baseline in each measure will be summarized using descriptive statistics. Missing data will be imputed using multiple imputation. Multiple imputation will be performed on actual values, domains, total scores, or summary scores depending on the endpoint. In addition, each clinical function measure will be analyzed using an ANCOVA model. The model may include covariates such as corresponding baseline value, baseline NfL, duration from onset of symptoms to the first dose of study treatment, and riluzole or edaravone use. The model will be used to estimate least-square (LS) means for each treatment group with standard errors (SEs), and LS mean differences between treatment groups with corresponding 95% confidence intervals (CIs). The p-values comparing treatment differences will also be presented.

[redacted]

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, treatment groups will be defined as Early-start BIIB105 (i.e., those who initiated BIIB105 in Part 1) and Placebo/Delayed-start BIIB105 (i.e., those who received placebo in Part 1), with baseline defined as Part 1 baseline. Clinical function data will be presented by the 120 mg dose level and treatment group (Cohort D1+D2 Early-start vs Placebo/Delayed-start). They will also be presented by cohort and treatment group as a sensitivity analysis (Cohort D1 Early-start vs Placebo/Delayed-start; Cohort D2 Early-start vs Placebo/Delayed-start).

[redacted]

13.3.5. Time to Death or Permanent Ventilation, Time to Death

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 each of the following start times:

1. Randomization in Study 275AS101 Part 1
2. Time of symptom onset

For time to death or permanent ventilation, and time to death, the median and percentiles and associated 95% confidence limits will be presented. P-values from log rank test and Cox regression model will be presented with the hazard ratio. The Cox model may include covariates such as corresponding baseline value, baseline NfL, duration from onset of symptoms to the first dose of study treatment, and riluzole or edaravone use.The log-rank test may be stratified by median baseline NfL.

Post-withdrawal or study completion vital status data will also be incorporated into a separate analysis of time to death.

[redacted] For analysis of integrated data from Part 1 and Part 2, analyses will be conducted to compare Early-start versus Placebo/Delayed-start treatment groups. [redacted]

[redacted]

[redacted]

[redacted]

13.4. Interim Analyses

One or more interim analyses of unblinded key safety, secondary, [redacted] endpoints (including PK, PD, clinical function) may be conducted following the completion of dosing of 1 or more dose cohorts in Part 1, to allow for the confirmation of dose escalation decisions and/or to inform decisions on the BIIB105 clinical development program.

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If, based on an interim analysis of Part 1, the Study Sponsor decides to terminate Part 1 of the study without terminating Part 2, participants who are active in Part 1 at the time of the Sponsor's decision will have the opportunity to end Part 1 and screen and enroll into Part 2. In this scenario, participants screening for Part 2 will not have to meet Section 6.1.2 Part 2 Inclusion Criterion #2 (having completed Part 1 through Week 25) to be eligible for Part 2.

Additional interim analyses may be performed during the conduct of Part 2, using data from Part 2 alone and/or integrated data from Part 1 and Part 2. Specifics will be detailed in the statistical analysis plan.

The participants, site staff, and Sponsor study team responsible for site monitoring and data management will remain blinded to treatment assignment during the ongoing data review, as well as during interim analyses, to minimize the potential for bias in the data cleaning process. Details will be provided in the Unblinding Plan and specific interim analysis plan.

13.5. Sample Size Considerations

Part 1:

The sample size of this first-in-human clinical study was selected with the goal of balancing between safety and tolerability considerations in dose escalation and obtaining sufficient initial information related to the safety and biological activities of BIIB105. Sample sizes of 6 participants receiving active treatment in lower dose Cohorts A and B will allow an [redacted]% or greater probability to observe at least 1 occurrence of an AE with event rates of [redacted]% or greater. The sample size of 9, 36, and 12 participants exposed to active doses in Cohorts C1, D1, and D2, respectively, allow an [redacted]% or greater probability to observe at least 1 occurrence of an AE with event rates of [redacted]%, or greater, respectively.

Cohort C2 will expose 3 participants with polyQ-ALS to active treatment as part of additional dose escalation step specifically for participants with intermediate-repeat CAG expansions in *ATXN2* gene as they may be more sensitive to the effects of BIIB105. The sample size of 3 was selected solely as precaution step before exposing participants with polyQ-ALS to 120 mg dose of BIIB105 in Cohort D2.

The sample size of Cohort D1 provides approximately [redacted]% power to detect a [redacted]% difference in the ratio to baseline in plasma NfL, in the BIIB105 versus placebo group, based on Cohort D1 120 mg data (N on BIIB105 = 36) vs pooled placebo data across Cohorts A through D1 (N = 19), with 2-sided [redacted]% significance level, assuming [redacted]% SD in both groups.

Part 2:

The sample size of Part 2 is based on the sample size of Part 1. Up to approximately 98 participants will be dosed in Part 2.

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14. ETHICAL REQUIREMENTS

The Sponsor, any contracted third party, 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 Investigators are responsible for demonstrating timely oversight of all clinical study data from their site, including data external to the electronic data capture system, such as laboratory, imaging, and electronic clinical outcomes assessment data. Investigators must approve all their data on completed CRFs by signing electronically, at the participant, visit, or casebook level, at any time prior to an interim lock or database lock, as well as before any subsequent re-lock. The electronic data capture system does not prohibit Investigator approval or signing in any way.

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

14.1. Declaration of Helsinki

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

14.2. 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 study sites in countries other than the United States.

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.

Sponsor 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 participant 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.

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

14.3. Changes to Final 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 14.4).

14.4. Informed Consent

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

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 and/or the participant's legally authorized representative. The participant and/or the participant's legally authorized representative must be given sufficient time to consider whether to participate in the study.

A copy of the signed and dated ICF must be given to the participant and/or the participant's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original and copies of the signed and dated ICFs.

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

When additional information that may affect participants' willingness to continue in the study becomes available, the Investigators will be notified in a timely manner, according to all local and applicable law. An updated ICF may be required.

The participant's informants/caregivers must also provide written informed consent to participate in the study. The original forms will be managed and archived in the same manner as the participants' ICFs, as described in Section 14.4.

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14.5. Participant Data Protection

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

During the study, participants' race and ethnicity will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or PK profile of the study treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity.

Study reports will be used for research purposes only. The 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.

14.6. Compensation for Injury

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

14.7. Conflict of Interest

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

14.8. Study Report Signatory

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

14.9. 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.

The Sponsor also will notify, when required, the regulatory authorities and ethics committees about the completion or termination of this study and send a copy of the study synopsis in accordance with necessary timelines.

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14.10. 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.

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15. KEY ROLES AND STUDY GOVERNANCE COMMITTEES

15.1. Vendors

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

15.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, management of SAE reports, monitoring, and data management.

15.1.2. 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.

15.1.3. Electronic Data Capture

Participant information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture tool configured by Sponsor and hosted by Metadata.

15.1.4. Digital Clinical Outcomes Data Capture

Participant information, including [redacted] and ventilation diary logs, will be captured electronically to assess clinical outcomes.

15.1.5. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by the Sponsor to analyze all hematology, coagulation testing, blood chemistry, and urine samples collected for this study, except for urine pregnancy tests and CSF, which will be analyzed by a local laboratory; repeat coagulation test will be analyzed by either the local laboratory or the central laboratory. A central laboratory will be utilized to test/confirm polyQ status for participation in Cohorts C2 and D2.

PK samples will be analyzed at a laboratory selected by the Sponsor. Duplicate PK samples will be collected in case the original sample is lost, damaged, or not evaluable.

The central laboratory will also receive, track, and ship all blood samples for specialized genotyping, PK and PD biomarker analysis, [redacted], and CSF samples for PK and PD biomarker analysis, including aliquots from these samples, retained as backup in case original samples are lost or not evaluable. Residual blood samples for future DNA testing will be processed to purify DNA and stored by the central laboratory.

15.1.6. Central Facility for Other Assessments

A central facility has been selected by the Sponsor to read and interpret all 12-lead ECGs for this study.

15.2. Study Committees

15.2.1. Safety Surveillance Team

The Sponsor's SST will serve as the study committee. The composition of the SST will follow Sponsor standard operating procedures. The SST, as described in Section 5.3, is responsible for reviewing the safety and PK data prior to dose escalation and at regular intervals in Part 2 and determining whether SAEs and clinically significant AEs result in cohort or study suspension.

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16. ADMINISTRATIVE PROCEDURES

16.1. Study Site Initiation

The Investigator must not screen any participants prior to completion of a study site initiation visit. This initiation visit with the Investigator and other site staff, as appropriate, will include a detailed review of the protocol, study procedures, and study responsibilities.

16.2. Quality Control and Quality Assurance

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

During and/or after completion of the study, quality assurance officers named by 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.

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

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

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

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16.4. Study Funding

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

16.5. Publications

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

16.6. 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 (if allowed per local regulations), 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 assessments at the study participant's home, which may include but are not limited to:

- Limited neurological examination
- Physical examination
- Vital signs
- Height and body weight collection
- [redacted]
- [redacted]
- [redacted]
- C-SSRS
- 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
- Review of concomitant medications and AEs

17. REFERENCES

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18. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 1/2 Multiple-Ascending-Dose Study With a Long-Term Open-Label Extension to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Effect on Disease Progression of BIIB105 Administered Intrathecally to Adults With Amyotrophic Lateral Sclerosis With or Without PolyCAG Expansion in the *ATXN-2* Gene," 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 (*DD MMM YYYY*)

_____

Investigator's Name (Print)

_____

Study Site (Print)

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AMENDMENT SUMMARY

Biogen Protocol 275AS101

A Phase 1/2 Multiple Ascending Dose Study With a Long-Term Open-Label Extension to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Effect on Disease Progression of BIIB105 Administered Intrathecally to Adults With Amyotrophic Lateral Sclerosis With or Without PolyCAG Expansion in the *ATXN2* Gene

Version 5.0

Date: 07 September 2023

EUDRA CT Number: 2020-000207-36

Version 5.0 of the protocol has been prepared for this amendment, which supersedes Version 4.0.

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PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 275AS101 is to add a new clinical drug product presentation.

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

Section 7.3, Study Treatment

Now reads:

BIIB105 is supplied as a sterile, buffered, and isotonic solution in **single-use clear** vials containing [redacted] ~~mg/mL of~~ study treatment ~~with~~**either at a concentration of** [redacted] **mg/mL and** a targeted volume of [redacted] mL per vial to ensure ~~a deliverable volume~~ **maximum withdrawal** of [redacted] mL for ~~withdrawal from the vial and~~ dose preparation, **or at a concentration of** [redacted] **mg/mL with a targeted volume of** [redacted] **mL per vial to ensure maximum withdrawal of** [redacted] **mL for dose preparation (once this presentation is available for use at clinical study sites). This is accompanied by** [redacted] **to be used as diluent where needed. Both BIIB105 and** [redacted] **vials are sealed with a butyl rubber stopper and aluminum over seal with flip-off cap**.

Rationale: The protocol is being updated to reflect changes in the BIIB105 manufacturing process. The manufacturing changes affect the study drug product presentation (concentration and volume) but do not have any impact on the final formulation of BIIB105 administered to study participants.

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SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 1.1, Synopsis

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

Section 5.2.2, Study Duration for Participants in Part 2

Change: Extended the maintenance dosing portion of the treatment period of Part 2 by up to approximately 52 weeks. The treatment period will be followed by the safety follow-up period as already defined in the protocol.

Now reads:

Study duration for each participant in Part 2 will be up to approximately ~~120~~**172** weeks:

- Screening Period of up to 4 weeks (for participants from Cohorts D1 and D2, Screening Period begins with Day 169 Visit of Part 1)
- Treatment Period of up to **approximately 156 weeks: either** 104 weeks**, OR until the last participant enrolled has had the opportunity for their Part 2 Day 365 visit (Week 52), whichever occurs later**
- Follow-up Period of approximately 12 weeks

Participants will have up to ~~31~~**approximately 44** CVs and ~~30~~**43** TCs during Part 2 of the study, which will include at least 1 Screening Visit, up to ~~28~~**approximately 41** Dosing Visits, 2 Follow-Up Visits, and up to ~~30~~**43** TCs.

Rationale: 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 until after the Part 1 final analysis has been completed.

This change also affects Figure 1, Study Design; Section 5.1.2, Study Overview Part 2; Section 5.3.2, Dosing Part 2; and Section 7.1, Regimen.

Section 5.4.2, Dose Termination

Change: Amended dose termination rules, including lifting them if SST review of Cohort D1 data supports continued dosing at the highest dose level.

Now reads:

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After evaluation of safety, tolerability, and PK data by the SST, Investigator, and if required, any ad hoc members, further dosing at the current level and dose escalation will be terminated if any of the following is observed:

- ~~Two~~**Three** similar SAEs (unless related to disease progression or unrelated to BIIIB105 upon medical review) are reported for participants receiving active study treatment within the same cohort.

- ~~Three~~**Four** or more similar AEs are reported for participants receiving active study treatment (unless related to disease progression or unrelated to BIIIB105 upon medical review) that are either not tolerable (as reported by the participant) or deemed a medically unacceptable risk by the SST.

- Sponsor requests that dosing be terminated.

Following the SST review of safety and PK data for Cohort D1 (Part 1), if there is agreement that the current emerging safety, tolerability, and PK data support continued dosing at 120 mg, the abovementioned dose termination rules will no longer apply. The Sponsor may still determine that a dose termination is required at any time due to emerging safety data.

Rationale: These changes update the scope and implementation of dose termination rules to reflect changes in study design from previous protocol amendments (Protocol Versions 3.0 and 4.0), as follows:

Increase in number of similar SAEs or AEs reported in participants receiving active study treatment to trigger dose termination:

This change reflects the increase in sample size with Protocol Version 4.0 (addition of 28 participants in Cohort D1, which increases the total number of participants in the 120 mg cohorts from 38 to 66).

End of dose termination rules after final SST review of Cohort D1 (Part 1):

This change aligns the dose termination rules with the cohort suspension rules, which were amended in Protocol Version 3.0.

With Protocol Version 3.0, the original study design (3-month first-in-human, placebo-controlled MAD study) expanded to become a 3- to 6-month placebo-controlled MAD study (Part 1) followed by a 2-year open-label long-term extension (Part 2). Therefore, Section 5.4.1 was amended to specify that the cohort suspension rules no longer apply if the SST agrees with continued 120 mg dosing after the final SST evaluation of Cohort D1 (Part 1), which assesses the benefit/risk profile of BIIB105 at the top dose in the study.

At the time of Protocol Version 3.0, the dose termination rules were not amended alongside the cohort suspension rules. However, the rationale for lifting the cohort suspension rules after the

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final SST evaluation of Cohort D1 (Part 1) also applies to the dose termination rules. Therefore, the dose termination rules are being amended to align with the cohort suspension rules.

Note that the SST will continue to review safety data from the study on an ongoing basis, and a dose termination may still be triggered at any time due to emerging safety data, as outlined in the protocol.

Section 13.3.1, Safety

Change: Updated how data will be analyzed and presented.

Now reads:

For analyses of Part 1, safety data will be summarized by **dose level and treatment assignment in Part 1 (BIIB105 5 mg [Cohort A], 20 mg [Cohort B], 60 mg [Cohorts C1+ C2], 120 mg [Cohorts D1+D2], Pooled Placebo 1+2), as well as by** cohort and treatment assignment in Part 1 (BIIB105-treated Cohorts A, B, C1, C2, D1, and D2; Pooled Placebo 1 and Pooled Placebo 2).

For analyses of Part 2, safety data will be summarized by dose level in Part 2 (BIIB105 60 mg vs BIIB105 120 mg). [redacted] ~~For integrated data from Part 1 and Part 2, safety data from the BIIB105-treated periods in Part 1 and Part 2 will be summarized by BIIB105 all doses combined (BIIB105 60 mg vs BIIB105 120 mg).~~ [redacted]

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, safety data from the BIIB105-treated periods in Part 1 and Part 2 will be summarized, with baseline defined as the first dose of 120 mg BIIB105, regardless of whether the participant started this dose in Part 1 or Part 2. [redacted]

To assess the overall safety profile of 60 mg BIIB105, integrated Part 1 and 2 safety data may be presented for any participant who received at least one dose of 60 mg BIIB105, with baseline defined as first dose of 60 mg BIIB105. To assess the overall safety profile of 120mg BIIB105, integrated Part 1 and 2 safety data may be presented for any participant who received at least one dose of 120 mg BIIB105, with baseline defined as the first dose of 120 mg BIIB105.

Rationale: To align language in the protocol with planned statistical analyses.

Section 13.3.2, Pharmacokinetics

Change: Updated how data will be analyzed and presented.

Now reads:

For analyses of Part 1, PK data will be summarized by dose level in Part 1 (BIIB105-treated ~~Cohorts A, B, C1 + C2, and D1 + D2). For integrated data from Part 1 and Part 2, PK data for~~

~~BIIB105-treated periods in Part 1 and Part 2 will be summarized by the 60 mg dose level in Part 1, 60 mg dose level in Part 2, 120 mg dose level in Part 1, and 120 mg dose level in Part 2.~~ **5 mg [Cohort A], 20 mg [Cohort B], 60 mg [Cohorts C1 + C2], and 120 mg [Cohorts D1 + D2]).**

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, PK data from the BIIB105-treated periods in Part 1 and Part 2 will be summarized, with baseline defined as the first dose of 120 mg BIIB105, regardless of whether the participant started this dose in Part 1 or Part 2. [redacted]

To assess the overall PK profile of 60 mg BIIB105, integrated Part 1 and 2 PK data may be presented for any participant who received at least one dose of 60 mg BIIB105, with baseline defined as first dose of 60 mg BIIB105. To assess the overall PK profile of 120mg BIIB105, integrated Part 1 and 2 PK data may be presented for any participant who received at least one dose of 120 mg BIIB105, with baseline defined as the first dose of 120 mg BIIB105.

Rationale: To align language in the protocol with planned statistical analyses.

Section 13.3.4, Clinical Function and Quality of Life Measures

Change: Updated how data will be analyzed and presented.

Now reads:

~~Cohorts C2 and D2 are a genetically defined subpopulation with potentially faster disease progression, and their data will be analyzed separately for clinical function and quality of life measures.~~ [redacted]

For integrated analyses of Part 1 and Part 2~~, clinical function data will be presented by cohort (Cohort A + B + C1, Cohort C2, Cohort D1,~~**for Cohorts D1** and ~~Cohort D2). Within these cohorts, the~~ **D2,** treatment groups will be defined as~~:~~ Early-start BIIB105 (i.e., those who initiated BIIB105 in Part 1) and Placebo/Delayed-start **BIIB105** (i.e., those who received placebo in Part 1)**,** with baseline defined as Part 1 baseline. **Clinical function data will be presented by the 120 mg dose level and treatment group (Cohort D1+D2 Early-start vs Placebo/Delayed-start). They will also be presented by cohort and treatment group as a sensitivity analysis (Cohort D1 Early-start vs Placebo/Delayed-start; Cohort D2 Early-start vs Placebo/Delayed-start).**

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[redacted]

Rationale: To align language in the protocol with planned statistical analyses.

This change also affects Section 4, Study Objectives and Endpoints; Section 5.2.1, Study Duration for Participants in Part 1; and Section 13.4, Interim Analyses.

Section 13.3.5, Time to Death or Permanent Ventilation, Time to Death

Change: Updated how data will be analyzed and presented.

Now reads:

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~~**each of** the following **start times**:

1. Randomization in Study 275AS101 Part 1
2. Time of symptom onset

For time to death or permanent ventilation, and time to death, the median and percentiles and associated 95% confidence limits will be presented. P-values from log rank test and Cox regression model will be presented with the hazard ratio. The Cox model may include covariates such as corresponding baseline ~~score~~**value**, baseline NfL, duration from onset of symptoms to the first dose of study treatment, and riluzole or edaravone use.The log-rank test may be stratified by median baseline NfL.

Post-withdrawal or study completion vital status data will also be incorporated into a separate analysis of time to death.

[redacted] For analysis of integrated data from Part 1 and Part 2, ~~data from all cohorts~~**analyses** will be ~~analyzed.~~**conducted to compare Early-start versus Placebo/Delayed-start treatment groups.** [redacted]

Rationale: To align language in the protocol with planned statistical analyses.

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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.
- Section 2, List of Abbreviations, was updated.
- Typographical errors and formatting were corrected.
- Table 2, Part 1 Schedule of Activities: Cohort D1 and D2: Footnote 4 was updated to include all TCs on days after nondosing LPs.
- Table 3, Schedule of Activities Part 2 (all Cohorts): New footnote 3 was added to clarify that TCs are only required after days on which an LP was performed. Also, the list of Maintenance Dose days was expanded to cover the new study duration, and a 3-day window was added for Dose 1 to reduce the risk of protocol deviation.Section 4, Study Objectives and Endpoints: An additional survival analysis was added to the [redacted] Endpoints.Section 5.1.2, Study Overview Part 2: SST review of Part 1, Cohort D2 data was added as a requirement for increasing Part 2 60 mg doses to 120 mg.
- Section 5.3.1, Dose Escalation Part 1: Added clarification that in the event of early study termination, a final SST will be held for Cohort D1 with all available safety data.
- Section 6.2.1, Exclusion Criteria Part 1: Updated exclusion criterion 21 to clarify that the benchmark is completion (not initiation) of Screening.
- Section 7.2, Study Treatment Management: Removed statement that the DHA supersedes all other references.
- Section 7.7.1.1, Allowed Concomitant Therapy: Clarified that riluzole and edaravone should not be initiated in Part 1.
- Section 7.7.1.2, Disallowed Concomitant Therapy: Called out sodium phenylbutyrate and taurursodiol specifically.
- Section 13.3.1.1, Adverse Events: Added a rationale for summarizing exposure-adjusted incidence rates

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LIST OF ABBREVIATIONS

aCSF	artificial cerebrospinal fluid
ADA	anti-drug antibody
AE	adverse event
ALS	amyotrophic lateral sclerosis
CAG	cytosine-adenine-guanine
CV	clinic visit
DHA	Directions for Handling and Administration
LP	lumbar puncture
MAD	multiple ascending dose
PK	pharmacokinetic(s)
polyQ	polyglutamine
RNA	ribonucleic acid
SAE	serious adverse event
SST	safety surveillance team
TC	telephone contact

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AMENDMENT SUMMARY

Biogen Protocol 275AS101

A Phase 1/2 Multiple-Ascending-Dose Study With a Long-Term Open-Label Extension to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Effect on Disease Progression of BIIB105 Administered Intrathecally to Adults With Amyotrophic Lateral Sclerosis With or Without Poly-CAG Expansion in the *Ataxin-2* Gene

Version 4.0

Date: 09 September 2022

EUDRA CT Number: 2020-000207-36

Version 4.0 of the protocol has been prepared for this amendment, which supersedes Version 3.0.

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PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 275AS101 is to increase the sample size in Cohort D1 from n = 20 to n = 48.

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

Section 13.5, Sample Size Considerations

Now reads:

Part 1:

The sample size of this first-in-human clinical study was selected with the goal of balancing between safety and tolerability considerations in dose escalation and obtaining sufficient initial information related to the safety and biological activities of BIIB105. Sample sizes of 6 participants receiving active treatment in lower dose Cohorts A and B will allow an [redacted]% or greater probability to observe at least 1 occurrence of an AE with event rates of [redacted]% or greater. The sample size of 9, ~~15~~**36**, and 12 participants exposed to active doses in Cohorts C1, D1, and D2, respectively, allow an [redacted]% or greater probability to observe at least 1 occurrence of an AE with event rates of [redacted]%, or greater, respectively.

…

The sample size ~~also allows for an estimate~~ of **Cohort D1 provides approximately [redacted]% power to detect a [redacted]% difference in** the ~~reduction of 120 mg of~~ **ratio to baseline in plasma NfL, in the** BIIB105 versus placebo ~~in CSF ATXN2 protein~~**group,** based on Cohort D1 120 mg data (N ~~= 15) and~~**on BIIB105 = 36) vs** pooled placebo data across Cohorts A~~, B, C1, and~~ **through** D1 (N ~~= 12)~~ **= 19),** with ~~a precision such that the width of the~~ 2-sided [redacted]**% significance level, assuming [redacted]% SD in both groups** ~~95% CI is within [redacted] fold of the geometric mean of active to placebo ratio in [redacted] month fold change from baseline. For example, if the observed geometric mean active to placebo ratio is [redacted] (i.e., [redacted]% reduction), the 95% CI would be ([redacted]).~~

Part 2:

> The sample size of Part 2 is based on the sample size of Part 1. ~~Approximately 70~~**Up to approximately 98** participants will be dosed in Part 2.

Rationale: The sample size increase will increase the study's power to investigate the safety, tolerability, PK, and effect on disease progression of 120 mg BIIB105 in ALS.

This change also affects Figure 1, Study Design; Section 5.1.1, (Study Overview) Part 1; and Section 5.3.1, Dose Escalation (Part 1).

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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~~.

Protocol Title

Change: Detail about the study structure, objectives, and phase was added.

Now reads:

A Phase 1**/2** Multiple-Ascending-Dose Study **With a Long-Term Open-Label Extension** to Assess the Safety, Tolerability, ~~and~~ Pharmacokinetics**, Pharmacodynamics, and Effect on Disease Progression** of BIIB105 Administered Intrathecally to Adults With Amyotrophic Lateral Sclerosis With or Without Poly-CAG Expansion in the *Ataxin-2* Gene

Rationale: The long-term OLE (Part 2) was not reflected in the title and evaluating the biomarker effect of BIIB105 is elevated to a secondary objective. Therefore, the overall phase of development of the study and title of the study were changed to reflect the study design, elevated objective, and related endpoints.

This change also affects Section 3.1, Study Rationale; Section 5.1, Study Overview; Section 18, Signed Agreement of the Study Protocol; and page headers.

Section 1.1, Synopsis

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

Section 3.2.2, Current Therapies for ALS

Change: Information on a newly approved ALS therapy was added.

Now reads:

~~There are no effective drug therapies to cure or substantially moderate functional decline or improve survival. Two treatments are currently approved for ALS.~~

Available treatments for ALS include riluzole, edaravone, and sodium phenylbutyrate and ursodoxicoltaurine, with approvals varying by region. Each has demonstrated modest effects on disease progression.

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In a 6-month randomized study in the United States, patients with ALS who received a combination of sodium phenylbutyrate and ursodoxicoltaurine demonstrated less decline in ALSFRS-R scores over 24 weeks compared with patients who received placebo [Paganoni 2020]. The mechanism of action of sodium phenylbutyrate in ALS is unknown, but its pharmacological activities include histone deacetylase inhibition and upregulation of heat shock proteins. The mechanism of action of ursodoxicoltaurine in ALS is also unknown, but its pharmacological activities include reduction of mitochondrial permeability.

Rationale: Updated to reflect current ALS therapy approvals in regions where the study is running.

Section 3.2.3.1, Nonclinical Experience

Change: Newly available data from fertility and fetal toxicity studies were summarized.

Now reads:

BIIB105 is not a genotoxicant as negative results were observed in the bacterial reverse mutation, in vitro chromosomal aberration, and in vivo rat micronucleus assays at limit concentrations/doses.

In a fertility study, there were no BIIB105-related effects on sperm concentration or morphology in male mice. In female mice, there were no BIIB105-related effects on female reproductive parameters, estrous cycle length, or precoital intervals. The NOAEL for reproductive toxicity was [redacted] mg/kg/dose. The corresponding serum exposure was a mean C_{max} of [redacted] µg/mL and a mean AUC_{0-24} of [redacted] µg*h/mL after repeat dosing in males. The exposures in pregnant females were a mean C_{max} of [redacted] µg/mL and a mean AUC_{0-24} of [redacted] µg*h/mL on GD [redacted].

In mice, BIIB105 did not result in any effects on embryo-fetal survival. A statistically significantly lower mean fetal weight was observed at [redacted] mg/kg/day and was considered adverse. BIIB105 did not produce any fetal external, visceral, or skeletal malformations or variations in mice. The NOAEL for developmental toxicity in mice was considered to be [redacted] mg/kg/dose, which corresponded to a mean C_{max} of [redacted] µg/mL and a mean AUC_{0-24} of [redacted] µg*h/mL in females. Fetal exposure, based on BIIB105 concentrations in liver, was approximately [redacted] times lower than the maternal C_{max}.

A dose level of [redacted] mg/kg/dose was considered to be the NOAEL for maternal toxicity and embryo-fetal development when BIIB105 was administered via SC injection to New Zealand White rabbits. This dose level was associated with a mean serum C_{max} of [redacted] µg/mL and a mean AUC_{last} of [redacted] µg*h/mL on GD [redacted]. There was no detectable BIIB105 in fetal livers in rabbit.

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Rationale: New reproductive toxicity nonclinical studies identified reproductive and developmental toxicity. These summaries were added to better inform potential safety risks.

This change also affects Section 3.3, Benefit-Risk Assessment.

Section 3.3, Benefit-Risk Assessment

Change: References to new nonclinical reproductive and developmental toxicity data and emerging clinical data from the ongoing study were added to the Benefit-Risk Assessment, and a Sponsor position on the benefit-risk profile was added.

Now reads:

~~Participants are not expected to receive therapeutic benefit from participation in the study.~~ **The potential benefit of BIIB105 in ALS has not been established. This** ~~The~~ study has been designed with appropriate dose escalation, safety monitoring, and stopping rules to minimize risks to participants. The results of this study may offer key insights into the development of a disease-modifying therapy for ALS.

This is a first in human study, thus the risk in humans is unknown. **Emerging clinical data can be found in the Investigator's Brochure.**

…

ALS is a debilitating, rapidly progressing, and life-threatening disease with a high unmet need for effective therapies. Overall, the benefit-risk profile is positive for the continued clinical development of BIIB105 for the treatment of ALS and polyQ-ALS.

~~Detailed information about the known and expected benefits and risks of BIIB105 is provided in the Investigator's Brochure and ICF. A high-level summary of those benefits and risks known during study design is provided here.~~

Rationale: These changes provide the Sponsor's position on the benefit-risk of developing BIIB105 for ALS and polyQ-ALS in the context of updated nonclinical data and emerging clinical safety data.

Section 4, Study Objectives and Endpoints

Change: CSF PK and plasma NfL were elevated from [redacted] to secondary endpoints. PD and biomarker endpoints were split out. Objectives and endpoints were separated out by study part (Part 1, Part 2) and prospectively defined for the integrated analyses (Integrated Part 1 and Part 2).

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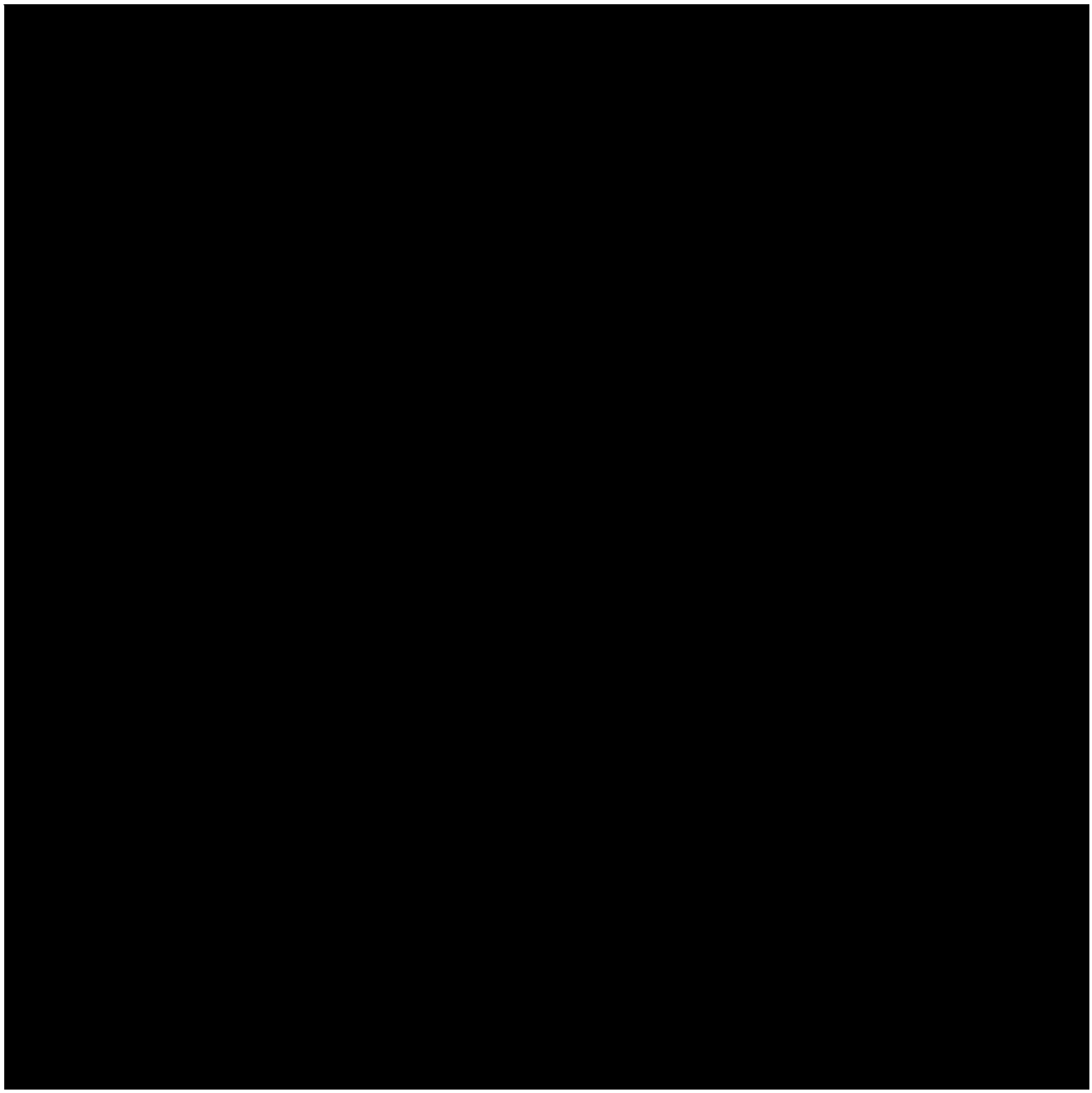
Now reads:

Part 1

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.	Incidence of AEs and SAEs **in Part 1**.
Secondary Objective	**Secondary Endpoints**
To assess the PK profile of BIIB105 in serum **and CSF** of participants with ALS or polyQ-ALS.	Serum **and CSF** concentrations of BIIB105 **in Part 1**. To evaluate the following serum PK parameters **in Part 1**: • AUC_{inf} • AUC_{last} • C_{max} • T_{max} • $t_{½}$
To evaluate the biomarker effect of BIIB105 in participants with ALS or polyQ-ALS.	**Secondary biomarker measure:** • **Changes from baseline in plasma levels of NfL in Part 1**
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the ~~PK profile~~**PD effect** of BIIB105 in ~~the CSF of~~ participants with ALS or polyQ-ALS.	**Exploratory PD measure:** • **Change from baseline in** CSF ~~concentrations~~**levels** of ~~BIIB105~~**ATXN2 protein in Part 1**.
[redacted]	



Part 2

Primary Objective	Part 2 Primary Endpoint
To evaluate the long-term safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.	**Incidence of AEs and SAEs in Part 2.**

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Integrated Part 1 and Part 2

Primary Objective	Primary Endpoint
To evaluate the long-term safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.	**Incidence of AEs and SAEs during the BIIB105-treated period in Part 1 and/or Part 2.**
Secondary Objective	**Secondary Endpoints**
To assess the long-term PK profile of BIIB105 in serum and CSF of participants with ALS or polyQ-ALS.	**Serum and CSF concentrations of BIIB105 in Part 1 and Part 2.** • **CSF trough PK concentration** • **Serum PK concentration if available**
To evaluate the long-term biomarker effect of BIIB105 in participants with ALS or polyQ-ALS, and to assess the impact of earlier initiation of BIIB105 (i.e., at start of Part 1) compared with delayed initiation of BIIB105 (i.e., at start of Part 2) on biomarkers.	**Secondary biomarker measure:** • **Changes from Part 1 baseline in plasma levels of NfL**
To evaluate the long-term effect of BIIB105 on measures of clinical function and to assess the impact of earlier initiation of BIIB105 (i.e., at start of Part 1) compared with delayed initiation of BIIB105 (i.e., at start of Part 2) on measures of clinical function.	**Changes from Part 1 baseline in the following assessments:** • **SVC** • **ALSFRS-R score** • **Muscle strength, as measured by HHD** **Survival analyses:** • **Time to death or permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days)**

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	• **Time to death** • **Time to death, incorporating post-study withdrawal or study completion vital status data**
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the long-term PD effect of BIIB105 in participants with ALS or polyQ-ALS, and to assess the impact of earlier initiation of BIIB105 (i.e., at start of Part 1) compared with delayed initiation of BIIB105 (i.e., at start of Part 2) on the PD measure.	**Exploratory PD measure:** • **Change from Part 1 baseline in CSF levels of ATXN2 protein.**
[redacted]	

Rationale: Elevating CSF PK and plasma NfL to secondary endpoints better reflects the goals of the study. Reorganizing the endpoints and objectives by study part helps to clarify the analysis strategy. Prospectively designing an integrated analysis plan will enable evaluation of early-start versus delayed-start BIIB105.

This change also affects Section 3.1, Study Rationale.

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Section 5.3.1, Dose Escalation (Part 1)

Change: Safety surveillance team review criteria for Cohorts D1 and D2 were updated.

Now reads:

For Cohort D1, the safety review will occur after the cohort is fully randomized, and at least 92 days have elapsed since the randomization and dosing of the 36th participant. ~~For Cohorts D1 and D2, the safety review for each cohort will occur after the cohort is fully randomized, and at least 92 days after the randomization of the 12th participant.~~ The SST will review all **available** blinded safety data from all randomized participants **in the cohort**, which must include a minimum of ~~12~~**33** evaluable participants (those who completed all of the first 5 dosing visits as well as the Day 92 clinic visit) ~~in each cohort~~. This review will be for a final safety review for Cohort~~s~~ D1 ~~and D2~~.

For Cohort D2, the safety review will occur after the cohort is fully randomized, and at least 92 days after the randomization of the 15th participant. The SST will review all available blinded safety data from all randomized participants in the cohort, which must include a minimum of 12 evaluable participants (those who completed all of the first 5 dosing visits as well as the Day 92 clinic visit). This review will be for a final safety review for Cohort D2. Should Part 1 be terminated early (per Section 5.2.1 and Section 13.4) prior to reaching randomization of the entire D2 cohort or minimal evaluable criteria as defined, a final safety SST will be held for Cohort D2 with all available safety data at the time of Part 1 termination.

Cohorts D1 and D2 can be reviewed concurrently or in separate SSTs, depending on when the cohorts have reached the minimum evaluable patients.

Principal Investigators from sites where participants were dosed will be included in the blinded safety data review. Review of blinded safety data may be followed by review of unblinded safety data of the current and preceding cohorts by the SST. Details of the unblinded review as well as the personnel to be unblinded to support dose escalation will be clearly defined in the Dose Escalation Plan and Unblinding Plan for this study.

In addition to the review of all safety data, there will be a review of available PK data collected through the third dose prior to dosing of the next dose cohort for Cohorts A, B, C1, and C2. For Cohort~~s~~ D1 ~~and D2~~, there will be a review of all available PK data for a minimum of ~~12~~**33** evaluable participants. **For Cohort D2, there will be a review of all available PK data for a minimum of 12 evaluable participants. Should Part 1 be terminated early (per Section 5.2.1 and Section 13.4) prior to reaching randomization of the entire D2 cohort or minimal evaluable criteria as defined, a final safety SST will be held for Cohort D2 with all available PK data at the time of Part 1 termination.**

Rationale: Criteria to initiate the SST safety review for Cohort D1 was updated to reflect the increased sample size for this cohort. The criteria to initiate the SST safety review for Cohort D2

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was corrected to reflect that at least 15 participants, not 12, should be randomized before the SST is held.

Section 6.1.2, (Inclusion Criteria) Part 2

Change: ICF requirements were updated.

Now reads:

1. Ability of the participant to ~~review the initial informed consent completed in Part 1,~~ understand the purpose and risks of the study and indicate ~~continued~~ **informed consent, and the ability of the participant or the participant's legally authorized representative to provide signed and dated informed** consent~~.~~ **and authorization to use protected health information in accordance with national and local privacy regulations.**

Rationale: A separate ICF will need to be signed for Part 2.

Section 6.2.1, (Exclusion Criteria) Part 1

Change: The minimum prescreening ALFRS-R slope requirement was removed for Cohort D1.

Now reads:

19. **In participants in Cohorts A, B, and C1, p**~~P~~rescreening ALSFRS-R slope > *-0.4* points/month, where prescreening ALSFRS-R slope is defined as ~~follows~~: (ALSFRS-R score at Screening – 48) / (months from date of symptom onset to date of Screening) ~~in participants from Cohorts A, B, C1, and D1~~. **This criterion is not applicable for Cohorts C2, D1, and D2.**

Rationale: The original intent of this exclusion criterion was to enrich the study population for faster-progressing participants, but ALSFRS-R prescreening slope has not been found to accurately predict disease progression due to nonlinear progression on the scale. Therefore, this exclusion criterion has been removed to allow participants who would otherwise be eligible to participate in the study.

Section 6.2.1, (Exclusion Criteria) Part 1

Change: A new exclusion criterion was added to restrict allowable ALS treatment for study participants.

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Now reads:

21. **Treatment with an approved disease-modifying therapy for ALS other than riluzole or edaravone within 1 month or 5 half-lives of therapy, whichever is longer, before Screening.**

Rationale: This change ensures that the concomitant disease-modifying medications for ALS that are allowed in Study 275AS101 Part 1 are consistent for all cohorts, to enable pooling of placebo data from participants across cohorts for analysis.

This change also affects Section 7.7.1.2, Disallowed Concomitant Therapy.

Section 6.2.2, (Exclusion Criteria) Part 2

Change: Language was added to permit participants who contracted HIV, HBV, or HCV during Part 1 to continue into Part 2 if appropriate.

Now reads:

1. History or positive test result at Screening for HIV. The requirement for testing at Screening may be omitted if it is not permitted by local regulations. **If participants from Cohorts D1 and D2 who would seamlessly roll from Part 1 into Part 2 test positive for HIV during screening for Part 2 but are clinically asymptomatic, they may enroll in Part 2 at the discretion of the Investigator.**

2. Current hepatitis C infection (defined as positive HCV antibody and detectable HCV RNA). Participants with positive HCV antibody and undetectable *HCV* RNA are eligible to participate in the study. **If participants from Cohorts D1 and D2 who would seamlessly roll from Part 1 into Part 2 test positive for hepatitis C during screening for Part 2 but are clinically asymptomatic, they may enroll in Part 2 at the discretion of the Investigator.**

3. Current hepatitis B infection (defined as positive for HbsAg and/or total anti-HBc). Participants with immunity to hepatitis B from previous natural infection (defined as negative HbsAg, positive anti-HBc, and positive anti-HBs) or vaccination (defined as negative HbsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study. **If participants from Cohorts D1 and D2 who would seamlessly roll from Part 1 into Part 2 test positive for hepatitis B during screening for Part 2 but are clinically asymptomatic, they may enroll in Part 2 at the discretion of the Investigator.**

Rationale: As participants in Cohorts D1 and D2 are anticipated to roll over seamlessly into the OLE, participants from these cohorts who happen to contract HIV, hepatitis B, or hepatitis C during Part 1 of the study and have been followed through Part 1 of the study and remain

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asymptomatic could have the option of continuing into the OLE at the discretion of the Investigator.

Section 6.3.3, Screen Failures

Changes: Language was updated to allow re-use of screening assessments that will not change over time.

Now reads:

Screen failures are defined as participants who sign the ICF but are not subsequently randomized. If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant's source documents and on the screening log. Participants who fail screening may be permitted to be rescreened once at the Investigator's discretion after discussion with the Sponsor. **All screening assessments would need to be repeated during rescreening except for the following:**

- **FSH level in female participants with postmenopausal state confirmed by level obtained in previous screening for this study**
- **For participants in Cohorts C2 or D2, confirmation of intermediate (30 to 33) CAG/CAA repeats in at least 1 allele in the *ATXN2* gene by the central laboratory, if available from previous screening for this study.**

Rationale: This change reduces participant burden and length of wait time between rescreening and Day 1 by allowing use of prior screening laboratory results that will not change over time (postmenopausal status, genetic testing) for rescreening purposes.

Section 11.2.11, Collection of Vital Status After Study Withdrawal and Completion

Changes: Language was added to permit optional collection of vital status.

Now reads:

11.2.11 Collection of Vital Status Before and After Study Withdrawal and Completion

Participants' vital status will be collected throughout the study. For participants who provide optional consent for data collection after study withdrawal or completion, follow-up on vital status and date of death (if deceased) will be performed.

Rationale: This change corrects an error in protocol version 3, where this data collection was added to the protocol but not to the list of assessments.

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Section 13, Statistical Methods and Determination of Sample Size

Changes: Language was added to clarify that separate analyses will be performed for separate Parts of the study and on integrated data. As part of this explanation, study populations were defined.

Now reads:

13.1 General Considerations

…

Analyses will be performed on data from Part 1 alone, data from Part 2 alone, and on integrated data from Part 1 and Part 2.

Placebo data in Part 1 may be pooled across cohorts for analyses. The Pooled Placebo 1 population is defined as participants from Cohorts A, B, C1, and D1 who received placebo in Part 1. The Pooled Placebo 2 population is defined as participants from Cohorts C2 and D2 who received placebo in Part 1.

13.2 Analysis Populations

13.2.1 Part 1

The **Part 1** ~~full analysis~~ **FAS** population is defined as all randomized participants~~.~~

~~The intent-to-treat (ITT) population is defined as all randomized subjects~~ who receive**d** at least 1 dose of study treatment **in Part 1. In analyses performed on the FAS, participants will be analyzed, based on the intent-to-treat (ITT) principle, according to their randomized treatment assignment regardless of treatment received**.

The **Part 1** safety analysis population is defined as all randomized participants who received at least 1 dose of study treatment **in Part 1**.

The **Part 1** PK analysis population is defined as all randomized participants who received at least 1 dose of study treatment and have at least 1 postdose serum and/or CSF BIIB105 measurement **in Part 1**.

The **Part 1** PD population is defined as subjects who received at least 1 dose of study treatment and have at least 1 available post-dose evaluation of the respective PD endpoint in the study **in Part 1**.

[redacted]

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13.2.2 Part 2

The Part 2 FAS population is defined as all enrolled participants who received at least 1 dose of study treatment in Part 2.

The Part 2 safety analysis population is defined as all participants who receive at least 1 dose of study treatment in Part 2

13.2.3 Integrated Part 1 and Part 2

Integrated data for Part 1 and Part 2 will be analyzed based on the following populations defined for Part 1, with the exception of the safety data, which will be defined separately: Part 1 FAS population, Part 1 PK population, Part 1 PD population, and Part 1 clinical function population.

The Integrated Part 1 and Part 2 safety analysis population is defined as all randomized participants who receive at least 1 dose of BIIB105 either in Part 1 or Part 2.

Rationale: This change provides clarity on planned analyses and pooling strategies.

Section 13.3, Methods of Analysis

Changes: Further detail was added, including handling of data from different parts of the study.

Now reads:

For analyses of Part 1, safety data will be summarized by cohort and treatment assignment in Part 1 (BIIB105-treated Cohorts A, B, C1, C2, D1, and D2; Pooled Placebo 1 and Pooled Placebo 2). For analyses of Part 2, safety data will be summarized by dose level in Part 2 (BIIB105 60 mg vs BIIB105 120 mg). [redacted]

For integrated data from Part 1 and Part 2, safety data from the BIIB105-treated periods in Part 1 and Part 2 will be summarized by BIIB105 all doses combined (BIIB105 60 mg vs BIIB105 120 mg). [redacted]

…

The relationship to study treatment will be classified as related or not related. **Exposure-adjusted incidence rates will also be summarized.**

…

Incidence of clinically relevant abnormalities and changes from baseline in ECGs will be summarized using frequency tables **and descriptive statistics**.

…

Serum and CSF BIIB105 concentrations will be summarized using descriptive statistics and, where warranted, plotted graphically over time both on linear and logarithmic scales. **For Part 1, summaries of BIIB105 PK parameters will also be summarized using descriptive statistics.**

For analyses of Part 1, PK data will be summarized by dose level in Part 1 (BIIB105-treated Cohorts A, B, C1 + C2, and D1 + D2). For integrated data from Part 1 and Part 2, PK data for BIIB105-treated periods in Part 1 and Part 2 will be summarized by the 60 mg dose level in Part 1, 60 mg dose level in Part 2, 120 mg dose level in Part 1, and 120 mg dose level in Part 2.

…

Similar analyses will also be performed for other biomarkers in the plasma, serum, and/or CSF, which may include but are not limited to NfL [redacted]. **For analyses of Part 1, data will be analyzed in a similar way as specified for clinical function endpoints. For analyses of integrated data from Part 1 and Part 2, data will be analyzed in a similar way as specified for clinical function endpoints.**

13.3.4 Clinical Function and Quality of Life Measures

The actual scores and changes from baseline in each measure will be summarized using descriptive statistics. **Missing data will be imputed using multiple imputation. Multiple imputation will be performed on actual values, domains, total scores, or summary scores depending on the endpoint.** In addition, each clinical function measure ~~may~~**will** be analyzed using ~~a mixed-effects repeated-measures~~**an ANCOVA** model. The model may include ~~dose group, visit, treatment-by-visit interaction, and~~**covariates such as corresponding** baseline score~~. Additional covariates may be included in the model for age, sex~~**, baseline NfL**, duration from onset of symptoms to the first dose of study treatment, and ~~site of onset~~**riluzole or edaravone use. The model will be used to estimate least-square (LS) means for each treatment group with standard errors (SEs), and LS mean differences between treatment groups with corresponding 95% confidence intervals (CIs). The p-values comparing treatment differences will also be presented.**

Cohorts C2 and D2 are a genetically defined subpopulation with potentially faster disease progression, and their data will be analyzed separately for clinical function and quality of life measures. **For analyses of Part 1, clinical function data will be presented by cohort and treatment assignment in Part 1 (BIIB105-treated Cohorts A, B, C1, C2, D1, and D2; Pooled Placebo 1 and Pooled Placebo 2). For integrated analyses of Part 1 and Part 2, clinical function data will be presented by cohort (Cohort A + B + C1, Cohort C2, Cohort D1, and Cohort D2). Within these cohorts, the treatment groups will be defined as: Early-start**

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BIIB105 (i.e., those who initiated BIIB105 in Part 1) and Placebo/Delayed-start (i.e., those who received placebo in Part 1) with baseline defined as Part 1 baseline.

13.3.5 Time to Death or Permanent Ventilation, Time to Death

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~~**Randomization in** Study 275AS101 Part 1
2. Time of symptom onset

For time to death or permanent ventilation, and time to death, the median and percentiles and associated 95% confidence limits will be presented. P-values from log rank test and Cox regression model will be presented with the hazard ratio. The Cox model may include covariates such as corresponding baseline score, baseline NfL, duration from onset of symptoms to the first dose of study treatment, and riluzole or edaravone use. The log-rank test may be stratified by median baseline NfL.

Post-withdrawal or study completion vital status data will also be incorporated into a separate analysis of time to death.

[redacted] **For analysis of integrated data from Part 1 and Part 2, data from all cohorts will be analyzed.**

Rationale: These changes provide additional detail about planned analyses.

Section 13.4, Interim Analyses

Changes: Language was added to describe early-termination scenarios and permit additional interim analyses.

Now reads:

One or more interim analyses of unblinded key safety, secondary, and [redacted] endpoints (including PK, PD, clinical function) may be conducted following the completion of dosing of 1 or more dose cohorts **in Part 1,** to allow for the confirmation of dose escalation decisions and/or to inform decisions on the BIIB105 clinical development program.

If, based on an interim analysis of Cohort D1 Part 1, the Study Sponsor decides to terminate Part 1 of the study for Cohort D2 without terminating Part 2, Cohort D2 participants who are active in Part 1 at the time of the Sponsor's decision will have the opportunity to end Part 1 and screen and enroll into Part 2. In this scenario, participants

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screening for Part 2 will not have to meet Section 6.1.2 Part 2 Inclusion Criterion #2 (having completed Part 1 through Week 25) to be eligible for Part 2.

Additional interim analyses may be performed during the conduct of Part 2, using data from Part 2 alone and/or integrated data from Part 1 and Part 2. Specifics will be detailed in the statistical analysis plan.

Rationale: This change provides an opportunity for Part 1 participants to continue to Part 2 even if an interim analysis leads to termination of Part 1.

This change also affects Section 5.2.1, Study Duration for Participants in Part 1; Section 5.6, End of Study; and Section 6.1.2, (Inclusion Criteria) Part 2.

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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 List of Abbreviations was updated.
- Typographical errors and formatting were corrected.
- Clarification of activities to be performed in Part 1 and/or Part 2 was added where appropriate.
- Section 1, Synopsis: the number of study sites was increased from 13 to 15 (also affects Section 5.1.1).
- Section 1, Schedule of Activities, Table 2:
  - Footnote 3 was updated to clarify that the Part 1 Day 169 Visit is not required to be the start of the screening period for Part 2.
  - Footnotes 4 and 9 were reworded for clarity.
  - Footnote 14 was updated to accommodate participants who may not physically be able to lay supine for 5 minutes (also applies to Section 9.1).
  - Footnotes 18, 20, 21, and 22 were updated to allow certain predose activities to be done up to 24 hours prior to LP.
  - Footnote 25 was updated to clarify that clinical laboratory samples should be collected predose and HbA1c is to be collected on Day 176 Visit, not Day 175.
  - Footnote 28 was updated to correct an error: 4-hour postdose urine sample is appropriate for urine metabolite analysis at both Day 1 and Day 169.
- Section 1, Schedule of Activities, Table 3:
  - "Review" was removed from the ICF tasks, as a new ICF will be provided and signed prior to Part 2.
  - [redacted]
  - Footnote 1 was updated to clarify that the Part 1 Day 169 Visit is not required to be the start of the screening period for Part 2.

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  - Footnote 10 was updated to accommodate participants who may not physically be able to lay supine for 5 minutes.

  - Footnotes 14, 16, 17, and 18 were updated to allow certain predose activities to be done up to 24 hours prior to LP.

  - Footnote 23 was updated to clarify that clinical laboratory samples should be collected predose; also, lipid panel and HbA1c should be collected at Screening.

- Section 3.1.2, Rationale for Starting Dose and Maximum Exposure (and throughout protocol), text was updated to reflect that recovery data are available for the 41-week NHP toxicology study.

- Table 4, Predicted *ATXN2* mRNA Reduction (Cortex and Spinal Cord), ATXN2 protein reduction (CSF), and Safety Margins at Steady-state at Proposed Dose Levels; the second column (Total Number of Participants per Dose Level) was removed to avoid confusion. This information is not crucial to this table and is presented more clearly elsewhere in the protocol.

- Section 15.2.1, Safety Surveillance Team: text was updated to reflect that the SST will additionally review the safety and PK data at regular intervals in Part 2 in addition to dose escalation in Part 1.

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LIST OF ABBREVIATIONS

AE	adverse event
ALS	amyotrophic lateral sclerosis
[redacted]	[redacted]
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
ATXN2	*ataxin-2* gene or RNA
ATXN2	ataxin-2 protein
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration time curve from time 0 to infinity
AUC_{last}	area under the concentration time curve from time 0 to time of the last measurable concentration
C_{max}	maximum observed concentration
CSF	cerebrospinal fluid
ECG	electrocardiogram
[redacted]	[redacted]
FAS	full analysis set
FSH	follicle-stimulating hormone
GD	gestation day
HbA1c	hemoglobin A1c
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HHD	handheld dynamometry
HIV	human immunodeficiency virus
ICF	informed consent form
[redacted]	[redacted]
LP	lumbar puncture
NfL	neurofilament light chain
NHP	nonhuman primate
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
[redacted]	[redacted]
polyQ	polyglutamine
RNA	ribonucleic acid
[redacted]	[redacted]
SAE	serious adverse event

SC	subcutaneous
SST	safety surveillance team
SVC	slow vital capacity
$t_{½}$	elimination half life
T_{max}	time to reach maximum observed concentration
[redacted]	[redacted]

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AMENDMENT SUMMARY

Biogen Protocol 275AS101

A Phase 1 Multiple-Ascending-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB105 Administered Intrathecally to Adults With Amyotrophic Lateral Sclerosis With or Without Poly-CAG Expansion in the *Ataxin-2* Gene

Version 3.0

Date: 18 November 2021

EUDRA CT Number: 2020-000207-36

Version 3.0 of the protocol has been prepared for this amendment, which supersedes Version 2.0.

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PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 275AS101 is to extend the Treatment Period for Cohorts D1 and D2 from approximately 13 weeks to approximately 25 weeks, and to add a second part to the study (Part 2, open-label long-term extension).

In Part 2, participants who complete 25 weeks in Part 1 of the study will receive up to 104 weeks of BIIB105, after which they will have an approximately 12-week Follow-Up Period.

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

Section 3.1, Study Rationale

Now reads:

Given the rapidly progressing, life-threatening, and rare nature of the disease as well as the high unmet medical need in ALS, the first-in-human Phase 1 study will be a ~~MAD evaluation of BIIB105 in adult participants with ALS and polyQ-ALS.~~ **two-part evaluation of BIIB105 in adult participants with ALS and polyQ-ALS. Part 1 will be a placebo-controlled MAD assessment of the safety, tolerability, and pharmacokinetics of BIIB105. Part 2 will be an extension study to assess the long-term safety, tolerability, pharmacokinetics, and effect on disease progression of BIIB105 in participants who complete Part 1 through Week 25 (Day 175 Visit for Cohorts A, B, C1, and C2; Day 176 Visit for Cohorts D1 and D2).**

This study design will minimize the number of participants receiving subtherapeutic doses and/or dosing durations. ~~The~~ **For all cohorts in Part 1, the** 72-hour safety data review following sentinel dosing of the first 2 participants of each dosing cohort and the 7-day safety review for each participant after administration of the first dose and prior to administration of the second dose will allow evaluation of potential acute safety and tolerability findings in each participant prior to the administration of additional doses, similar to a single-ascending-dose study design. **Part 2 will provide up to 104 weeks of dosing of BIIB105 for study participants who complete 25 weeks in Part 1. The safety, PK, PD, and clinical function data collected from Part 2 will allow for the understanding of the long-term effect of BIIB105 in participants with ALS and polyQ-ALS.**

Rationale: The Treatment Period duration was extended from 13 to 25 weeks in the 120 mg dose cohorts (Cohorts D1 and D2) to evaluate the longer-term safety of BIIB105 versus placebo and to enable detection of a biomarker and/or clinical effect of BIIB105 in adults with ALS and polyQ-ALS at this dose level.

The long-term extension portion of the study (Part 2) was added to enable assessment of the long-term safety, tolerability, pharmacokinetics, and effect on disease progression of BIIB105 in adults with ALS and polyQ-ALS.

There will be 2 dose levels in Part 2 of the study:

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- Cohort A, B, C1, and C2 participants will receive 60 mg in Part 2.
- Cohort D1 and D2 participants will receive 120 mg dosing in Part 2.

This change also affects the Schedule of Activities, Tables 2 and 3; the Study Design Schematic; Section 5.1, Study Overview, Section 5.2, Study Duration for Participants; Section 5.3, Dosing; Section 6, Study Population; Section 6.3.1, Screening; Section 7, Study Treatment; Section 7.5, Precautions; Section 9.1, Clinical Assessments; and Section 13.5, Sample Size Considerations.

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SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 1.1, Synopsis

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

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Section 1, Schedule of Activities, Table 2, Part 1 Scheduled of Activities: Cohort D1 and D2

[redacted]

Now reads:

	Screening[1]	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Doses 4, 5, 6, 7	TC	CV	TC	Dose 8	TC	CV	TC	FU Period[2]				
																					CV	TC	Final/ ET Visit	TC	
Days		1		2	8 (±2)	15 (±3)	16 (+1)	22 (±3)	29 (±3)	30 (+1)	36 (±3)	50 (±3)	57, 85, 113, 141 ((±3)	58, 86, 114, 142 (+1)	64, 92, 120, 148 (±3)	78, 106, 134, 162 (±3)	169 (±3)[3]	170 (+1)	176 (±3)	177 (+1)[4]	214 (±3)	215 (+1)	259 (±3)	260 (+1)	UV
Assessments[5]	-28 to -1	Predose	Dosing/Postdose	(24 ±1 h) postdose																					

[redacted]

Section 3.1.2, Rationale for Starting Dose and Maximum Exposure

Change: New nonclinical study information was added.

Now reads:

A single-dose NHP toxicity study ~~(P105-19-06)~~ identified a maximum tolerated dose ([redacted] mg) and reversible AEs at [redacted] mg, which can be monitored clinically. Specifically, [redacted] of [redacted] animals dosed at [redacted] mg exhibited increased muscle tone, whole body spasms, and tremors that required administration of diazepam. The animal fully recovered by [redacted] hours. Additional nonclinical NHP data was obtained from a 13-week study with [redacted] doses of BIIB105 administered at [redacted] mg **and a 41-week study with [redacted] doses of BIIB105 administered at [redacted] mg.**

BIIB105 was tested in 2 pharmacologically relevant species: NHP and mouse. Because BIIB105 produced no adverse effects at any of the dose levels used in the [redacted] repeat-dose GLP studies, the highest dose of each study was identified as the NOAEL. Specifically, the NOAEL for the 13-week monkey IT study is [redacted] mg, the NOAEL for the **41-week monkey IT study is [redacted] mg (pending recovery data), the NOAEL for both the** 14-week**, and 26-week** mouse SC ~~study~~ **studies** is [redacted] mg/kg, and the NOAEL for the 57-day mouse ICV study is [redacted] mg. The NHP was deemed the most sensitive species because dose-limiting effects were identified in a GLP single-dose NHP study at [redacted] mg, whereas no dose-limiting toxicities have been identified in the rodent studies. ~~The~~ **At the time of selection of the starting dose for this study, the** 13-week NHP study also provided the lowest HED, which was calculated to be [redacted] mg utilizing a CSF volumetric scaling factor of 10. This ~~represents~~ **represented** the most conservative estimate based on CSF volume ratio between humans and NHPs and as compared with the HED in the mouse ICV ([redacted] mg) and mouse SC ([redacted] mg or [redacted] mg/kg based on a [redacted] kg human) toxicity studies.

Therefore, the selection of the starting dose for **Part 1 of** this study is based on the NOAEL dose of [redacted] mg, established in the 13-week toxicology study in cynomolgus monkeys, and on the expected PD of BIIB105 in the brain cortex and spinal cord. The HED value was divided by the conventional safety factor of 10 to yield the MRSD of [redacted] mg. The proposed [redacted] mg starting dose is below the MRSD, has a [redacted]-fold safety factor over the HED ([redacted] mg) of the NOAEL from the 13-week toxicology study, and is expected to produce minimal to moderate pharmacologic effects in the brain and spinal cord.

There were 2 chronic toxicology GLP studies conducted to support the dosing duration for Part 2 of this study. In the 41-week NHP study BIIB105 was administered IT ([redacted] mg) on Days [redacted], then [redacted] until Day [redacted]. The dosing period of the study has completed and recovery period is ongoing. In the 26-week mouse study BIIB105 was administered SC ([redacted] mg/kg/dose) every [redacted] from Day [redacted] through Day [redacted]. NOAEL for both of the studies was considered to be the highest dose tested (pending recovery data in the NHP study). The 41-week NHP chronic toxicology study provided the lowest HED, which was calculated to be [redacted] mg utilizing a CSF volumetric scaling factor of 10. These chronic toxicology studies support the proposed dose levels and dosing duration in the study.

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…

The predicted *ATXN2* mRNA reductions in the target CNS regions and safety margins ~~after [redacted]-dose administrations~~ **at steady state** at the proposed dose levels planned in this study are shown in Table 4. The MRSD of [redacted] mg is estimated to reduce *ATXN2* mRNA levels approximately [redacted]% in the cortex and approximately [redacted]% in the spinal cord after [redacted]~~-doses.~~ **reaching steady state.** In consideration of the higher reduction of *ATXN2* mRNA in the spinal cord, a starting dose of [redacted] mg is proposed, which is anticipated to reduce *ATXN2* mRNA levels by approximately [redacted]% in the cortex and [redacted]% in the spinal cord. A maximum dose of [redacted] mg is proposed at this time and is estimated to reduce *ATXN2* mRNA levels in the cortex by approximately [redacted]% and in the spinal cord by approximately [redacted]% at steady state and will provide an approximately [redacted]-fold safety margin to the HED ([redacted] mg) of the **13-week** NHP **IT toxicology study** NOAEL ([redacted] mg)~~.~~ **and an approximately [redacted]-fold safety margin to the HED ([redacted] mg) of the 41-week NHP IT toxicology study NOAEL ([redacted] mg- pending recovery data).** Postmortem tissue analyses from the 13-week **and 41-week** toxicology ~~study~~ **studies** in NHP showed that the CNS tissue ATXN2 protein levels are reflective of CNS tissue *ATXN2* mRNA levels. [redacted]

The length of the dosing interval during the 28-day loading period (3 doses administered once every 2 weeks) ~~will potentially~~ **is designed to** yield a rapid onset of steady-state exposure~~. After~~ **by the third dose on Day 29. Following** the loading period, ~~the MAD design, with 2 maintenance doses administered once~~ **dosing** every 4 weeks~~, will allow for the evaluation of longer-term tolerability at~~ **is projected to maintain** steady-state **exposure based on the whole-body physiologically based PK model.**

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Table 4: Predicted *ATXN2* mRNA Reduction **(Cortex and Spinal Cord), ATXN2 Protein Reduction (CSF),** and Safety Margins ~~After 5 Administrations~~ at Steady-state at Proposed Dose Levels

~~Indication~~	~~Cohort~~	Dose (mg)	Total Number of Participants per ~~Cohort~~ **Dose Level**	Fold Increase	% Decrease in Cortex Average (maximum)	% Decrease in Spinal Cord Average (maximum)	**% Decrease in CSF (approximate median)**	Safety Margin1 **13 week/ 41 week**
[redacted]	~~A~~	5	8	[redacted]				
	~~B~~	20	8					
	~~C1~~	~~60~~	~~12~~					
	~~D1~~	~~120~~	~~20~~					
[redacted]	~~C2~~	60	4**16**					
	~~D2~~	120	~~18~~**38**					

[1]Safety margins are based ~~in~~ **HED of the NOAEL 13 week and 41 weeks NHP IT toxicology studies using** CSF volumetric scaling.

During **Part 1 of** the study, the SST will review safety, tolerability, and available PK data before each dose escalation.

Rationale: This section was updated to reflect new data from the 41-week NHP chronic toxicology study, which resulted in a NOAEL of [redacted] mg (pending data from the recovery portion of the study, which is ongoing at the time of this protocol amendment). The rationale for maximum exposure was updated to reflect the revised safety margins of doses tested in Study 275AS101 to the 41-week NHP NOAEL at steady state.

This change also affects Section 3.2.3.1, Nonclinical Experience.

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Section 4, Study Objectives and Endpoints

[redacted].

Now reads:

To evaluate the effect of BIIB105 on measures of clinical function**.**

Changes from baseline in the following assessments:

- SVC
- ALSFRS-R score
- Muscle strength, as measured by HHD
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

Section 5.1, Study Overview

Change: The natural history run-in period for Cohort D2 was removed from the protocol.

Now reads:

Adult participants with ALS will be randomized at a ratio of 3:1 (active drug:placebo) in Cohorts A, B, C1, and D1. Adult participants with polyQ-ALS will be randomized at a ratio of 3:1 in Cohort C2 and at a ratio of 2:1 in Cohort D2. Cohorts C1 and C2 can dose concurrently. Cohorts D1 and D2 can dose concurrently~~, but participants with polyQ-ALS (Cohort D2) must complete a 4-month or longer Natural History Run-in Period (inclusive of the Screening Period) prior to dosing. Participants with polyQ-ALS (Cohort D2) may be enrolled (i.e., sign the main ICF) in the study and enter the Natural History Run-in Period prior to the SST approving the safety of Cohort C2 and allowing the dosing of Cohort D2; dosing of Cohort D2 will not begin until after SST approval is obtained as described in Section 5.3. The Natural History Run-in Period will be included to gain a better understanding of the natural history of polyQ-ALS and an enhanced ability to detect clinical changes in a small population with limited ease of access~~.

Rationale: Given the potential importance of early treatment initiation in ALS, the natural history run-in period for Cohort D2 was removed to allow investigation of the effect of BIIB105 initiated approximately 4 months earlier in polyQ-ALS. PolyQ-ALS participants may begin dosing immediately after screening is completed and eligibility is confirmed. PolyQ-ALS participants who are actively enrolled in the Cohort D2 natural history run-in period at the time that the protocol amendment is approved will not have to complete the full run-in period and may immediately enter the screening period for the study.

This change also affects Section 5.2.1, Study Duration for Participants in Part 1; Section 12.3, Monitoring and Recording Events.

Section 5.2.2, Study Duration for Participants in Part 2

Change: Language was added allowing follow-up of health status after withdrawal from or end of study, if a participant consents to data collection after withdrawal or study completion.

Now reads:

…

After a participant's end of study date, follow-up on vital status and date of death (if deceased) will be performed for participants who provide optional consent for data collection after study completion.

Rationale: This text was added to enable follow-up of health status, such as vital status and date of death (if deceased) after participant withdrawal from study or study completion for analyses of BIIB105 effect on survival.

This change also affects Section 5.6, End of Study; Section 8.3, Withdrawal of Participants From the Study.

Section 5.3.1, Dose Escalation (Part 1)

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Change: Safety surveillance team review criteria for Cohorts D1 and D2 was separated from the criteria for Cohorts A, B, C1, and C2.

…

For Cohorts D1 and D2, the safety review for each cohort will occur after the cohort is fully randomized, and at least 92 days after the randomization of the 12th participant. The SST will review all blinded safety data from all randomized participants, which must include a minimum of 12 evaluable participants (those who completed all of the first 5 dosing visits as well as the Day 92 clinic visit) in each cohort. This review will be for a final safety review for Cohorts D1 and D2. Cohorts D1 and D2 can be reviewed concurrently or in separate SSTs, depending on when the cohorts have reached the minimum evaluable patients.

…

In addition to the review of all safety data, there will be a review of available PK data collected through ~~6 hours after~~ the third dose ~~on Day 29~~ prior to dosing of the next dose cohort **for Cohorts A, B, C1, and C2. For Cohorts D1 and D2, there will be a review of all available PK data for a minimum of 12 evaluable participants.**

Rationale: Criteria to initiate SST safety reviews for Cohorts D1 and D2 were updated to reflect the longer length of the study for these two cohorts.

Section 5.4.1, Cohort Suspension

Change: Cohort study stopping rules were updated to include additional information on the role of the SST.

Now reads:

If 1 participant experiences either an SAE or a medically unacceptable AE (as defined by the Investigator or the Sponsor), the Sponsor Medical Director and Global Medical Safety Physician will ~~discuss the event with~~ **review relevant safety information and obtain more information from** the Investigator ~~and review the SAE form (~~if ~~applicable).~~ **necessary.** If the AE is assessed as unrelated to study treatment by both the Investigator and the Sponsor (e.g., is a known sign or symptom of ALS or is a known effect of the LP procedure), dose suspension is not necessary.

If the SAE or medically unacceptable AE (as determined by the Investigator or the Sponsor) is assessed as related to study treatment by the Investigator or the Sponsor~~, all~~ **then** dosing **at and above the dose level at which the event occurred** will be suspended until the event has been fully evaluated by the SST.

…

Following the SST review of safety and PK data for Cohort D1 (Part 1), if there is agreement that the current emerging safety, tolerability, and PK data support continued

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dosing at 120 mg, the abovementioned dose suspension rules will no longer apply. The Sponsor may still determine that a dose suspension is required at any time due to emerging safety data.

Rationale: Cohort study stopping rules were updated to reflect the addition of Part 2. Because some participants may be dosed with 60 mg in Part 2 while other participants are being dosed with 120 mg (in Part 1 or 2), there may be more than one active dose level in the study at the time of a potential SAE or medically unacceptable AE. The dosing suspension rules were updated to specify that dose suspension would apply to any dose at or above the dose level at which an SAE or medically unacceptable AE was assessed as related to study treatment. The automatic dose suspension rules will end after SST evaluation of Cohort D1 (Part 1), if the SST agrees with continued 120 mg dosing in the study, because benefit/risk profile of BIIB105 at the top dose will have been assessed, and because participants in the study will be moving from the first-in-human portion of the study into the long-term extension portion of the study without further dose escalation.

Section 5.4.3, Study Termination

Changes: Study termination criteria were clarified.

Now reads:

...

If, in light of emerging data, the Sponsor decides to continue testing, evaluation, or development of the product only for a specific subpopulation of ALS (for example, polyQ-ALS), the study may be terminated for participants who do not meet criteria for the subpopulation.

Rationale: The study termination rules were updated to reflect that a decision for BIIB105 development to proceed only for a subpopulation of ALS would result in the study continuing only for that subpopulation of ALS.

Section 6.1, Inclusion Criteria

Change: Part 1 inclusion criteria 1, 10, and 11 were updated.

Now reads:

6.1.1 Part 1

1. Ability of the participant ~~and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and applicable,~~ to understand the purpose and risks of the study~~, to provide~~ **and indicate** informed consent, and ~~to authorize~~ the **ability of the participant or the participant's legally authorized representative, to provide signed and**

dated informed consent and authorization to use ~~of confidential~~ **protected** health information in accordance with national and local privacy regulations.

…

10. Screening values of coagulation parameters including platelet count, INR, PT, and APTT should be within normal ranges. **Coagulation tests done at a local laboratory may be used for screening purposes, in order to reduce participant burden.** Coagulation tests may be repeated once at the local laboratory if, in the opinion of the Investigator, values of the initial tests are out of range but 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 and after a consultation with the Sponsor.

11. Has an informant/caregiver who, in the Investigator's judgment, has frequent and sufficient contact with the participant as to be able to provide accurate information about the participant's cognitive and functional abilities at Screening. An informant/caregiver should be available at Screening ~~(or at the Day -113 Visit for participants in Cohort D2), and the~~**The** participation of the same informant/caregiver for the duration of the study is encouraged.

…

Rationale: The change to inclusion criterion 1 was made to clarify that, while the participant's representative may sign the consent form on the participant's behalf, the representative may not provide informed consent on the participant's behalf. The participant must have the ability to understand the purpose and risks of the study and indicate consent.

The change to inclusion criterion 10 was made to clarify that coagulation tests completed at a local laboratory may be used for screening purposes, thereby reducing participant burden.

For inclusion criterion 11, there is no longer a requirement for a caregiver at Day -113 because the natural history portion of the study for Cohort D2 participants was removed.

Section 6.3.3, Screen Failures

Change: A rescreening option was added for screen failures.

Now reads:

If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant's source documents and on the screening log. **Participants who fail screening may be permitted to be rescreened once at the Investigator's discretion after discussion with the Sponsor.**

...

Rationale: This language was added to clarify procedures for re-screening in the case of screen failures.

Section 7.7.1.2, Disallowed Concomitant Medication

Change: Text was updated to state that indwelling injection ports/catheters are prohibited only during Part 1 of the study.

Now reads:

...

Use of a diaphragm pacing system, ~~indwelling injection ports/catheters,~~ investigational drugs other than the investigational product (including drugs for ALS through compassionate use programs), or ASOs is prohibited for the duration of the study.

Use of indwelling injection ports/catheters are prohibited during Part 1 of the study.

Rationale: Because indwelling injection ports/catheters are becoming more commonly used in the clinical care of ALS patients, injection ports/catheters will be allowed only during Part 2 of the study for participants from all cohorts.

Indwelling injection ports/catheters will remain prohibited during Part 1 of the study to ensure that participants from Cohorts D1 and D2 are comparable to those in Cohorts A, B, C1, C2 (who were also prohibited from having indwelling injection ports/catheters during Part 1), for the purposes of safety monitoring and pooling of placebo data.

This change also affects Section 6.2, Part 1 exclusion criterion 16.

Section 9.1, Clinical Assessments

Change: Information was updated to clearly reflect Part 1 and Part 2 assessment requirements.

Now reads:

The following clinical assessments will be performed to evaluate the safety profile of BIIB105:

- ...
- C-SSRS:

– **In Part 1, the** "Since Last Visit" version of C-SSRS will be used from Day 8 onward.

– **In Part 2, participants from Cohorts D1 and D2 will use "Since Last Visit" version of C-SSRS on Day 1 onward. Participants from Cohorts A, B, C1, and C2 will use the "Since Last Visit" version of the C-SSRS from Day 15 onward.**

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Rationale: Details about the C-SSRS versions to be used at visits were updated to reflect the addition of Part 2.

Section 11.2, Clinical Functional Assessments

[redacted]

Now reads:

[redacted]

- SVC
- **ALSFRSR (standard)**
- [redacted]
- HHD
- [redacted]
- **Ventilation diary**

11.2.2 ALS Functional Rating Scale-Revised (standard)

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. ~~This~~ **In Part 1, this** study site staff member will remain blinded to participants' treatment assignments and to the results of other assessments. **In Part 2, this study site staff member will remain blinded to participants' treatment assignments and to the**

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results of other assessments during the blinded loading dose period for participants in Cohorts D1 and D2.

[redacted]

[redacted]

[redacted].

Section 11.2, Clinical Functional Assessments

Change: Text was added specifying that participants will complete a weekly ventilation e-diary.

Now reads:

11.2.10 Participant Ventilation Diary

Participants will be given diaries to record use of ventilation. This diary will be reviewed with study site staff at each visit. Refer to the Study Reference Guide for details.

Rationale: The ventilation diary was added to enable analyses of the effect of BIIB105 on time to death or permanent ventilation (i.e., survival without permanent ventilation).

This change also affects Section 1, Schedule of Activities Tables 2 and 3.

[redacted]

[redacted]

Section 13.2, Analysis Populations

Change: Text was added defining the analysis populations.

Now reads:

The full analysis population is defined as all randomized participants.

The intent-to-treat (ITT) population is defined as all randomized subjects who receive at least 1 dose of study treatment.

The safety analysis population is defined as all randomized participants who receive at least 1 dose of study treatment.

The PK analysis population is defined as all randomized participants who receive at least 1 dose of study treatment and have at least 1 postdose serum and/or CSF BIIB105 measurement.

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

The clinical function set is defined as the subset of the ITT population who have at least 1 post-dose measurement.

Any additional details will be specified in the statistical analysis plan.

Rationale: This section was updated to reflect the planned analysis populations for the study.

Section 13.3.1.1, Adverse Events

Change: Details were added to clarify the planned statistical analyses of AEs.

Now reads:

AEs will be coded using the Medical Dictionary for Regulatory Activities **(MedDRA)**. The incidence of treatment-emergent AEs, SAEs, **deaths** and AEs leading to treatment discontinuation**, at minimum,** will be ~~tabulated by dose level, with placebo data pooled across cohorts~~ **summarized by system organ class and preferred term. The AEs level of severity and relationship to study treatment will also be similarly summarized. For the summary of AEs by severity, if a subject 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.**

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Rationale: This section was updated to reflect the planned statistical analyses for the study.

Section 13.3.1.2, Laboratory Results

Change: Details for planned laboratory analyses were added.

Now reads:

Laboratory **data includes hematology, coagulation, blood chemistry, CSF assessments, and urinalysis, and** will be summarized~~, with placebo data pooled across cohorts~~. Summary statistics for actual values and changes from baseline will be presented for quantitative laboratory data. In addition, shift tables will be used to tabulate the shifts from baseline to high/low status for each laboratory test.

Rationale: This section was updated to clarify details of the planned statistical analyses for the study.

Section 16.6, Public Health Emergencies

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

Now reads:

16.6 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 (if allowed per local regulations), 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 assessments at the study participant's home, which may include but are not limited to:

- **Limited neurological examination**

- **Physical examination**
- **Vital signs**
- **Height and body weight collection**
- [redacted]
- [redacted]
- [redacted]
- **C-SSRS**
- **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**
- **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.

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Section 15.1.4, Digital Clinical Outcomes Data Capture

Change: A section was added to account for the digital data collected by participants.

Now reads:

15.1.4 Digital Clinical Outcomes Data Capture

Participant information, including [redacted] and ventilation diary logs, will be captured electronically to assess clinical outcomes.

Rationale: [redacted] and the ventilation e-diary will be accessible via digital devices given to the participants.

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SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected.
- Section 1, Schedule of Activities, Table 1, a safety telephone call was added after the final or early termination visit. Information in the Notes column was moved to the footnotes. The title of the table was also updated to reflect that the assessments were only for Cohorts A, B, C1, and C2 in Part 1.
- Section 1, Schedule of Activities, Table 2:
  - Footnote 11 was updated to include specific days a limited physical examination will take place.
  - Footnote 12 was updated to provide sites an appropriate time window (±15 minutes) to complete study assessments on dosing days.
  - Footnote 14 was updated to provide sites an appropriate time window (±15 minutes) to complete ECG and vital signs on dosing days. Text was also added to clarify how vital signs and ECGs should be administered.
  - Footnote 25 was updated to add Day 259 to HbA1c and lipid panel assessment.
  - Footnote 26 was updated to clarify time window for serum sampling for PK postdose on dosing days. Text was also added to clarify that remaining serum may be used for [redacted].
  - Footnote 27 was added to clarify that assessment should take place on Day 85 visit only.
  - Footnote 29 was updated to clarify that remaining CSF sample may be used for [redacted].
- Section 3.2.3, Profile of Previous Experience with BIIB109, and Section 3.2.3.2, Clinical Experience, text was updated to reflect that clinical data are available for BIIB105.
- [redacted]

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- Section 13.3.1.3, Vital Signs; Section 13.3.1.4, C-SSRS; and Section 13.3.1.5, Electrocardiogram, text was edited to remove the term “dose level” from the description of these assessments.

- Section 13.3.3, Pharmacodynamics, text was updated to clarify analysis for pharmacodynamics.

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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
CAG	cytosine-adenine-guanine
CNS	central nervous system
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CV	clinic visit
DNA	deoxyribonucleic acid
ECG	electrocardiogram
[redacted]	[redacted]
ET	early termination
HbA1c	hemoglobin A1c
HED	human equivalent dose
HHD	handheld dynamometry
ICF	informed consent form
INR	international normalized ratio
[redacted]	[redacted]
IT	intrathecal(ly)
LP	lumbar puncture
MAD	multiple-ascending dose
mRNA	messenger ribonucleic acid
MRSD	maximum recommended starting dose
NHP	nonhuman primate
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
polyQ	polyglutamine
PT	prothrombin time
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SST	safety surveillance team
SVC	slow vital capacity
TC	telephone contact
UV	Unscheduled Visit

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[redacted]	[redacted]

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AMENDMENT SUMMARY

Biogen Protocol 275AS101

A Phase 1 Multiple-Ascending-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB105 Administered Intrathecally to Adults With Amyotrophic Lateral Sclerosis With or Without Poly-CAG Expansion in the *Ataxin-2* Gene

Version 2

Date: 02 March 2021

EUDRA CT Number: 2020-000207-36

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

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PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 275AS101 is to clarify the dosing of the sentinel pair in cohort C2 to avoid the possible unblinding of study participants' treatment assignment.

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

5.1, Study Overview

Now reads:

[…]

The first 2 participants ~~within each~~ **in all cohorts, except** cohort **C2**, will be randomized at a ratio of 1:1 (active:placebo) and dosed as a sentinel group. No other participants within the cohort will be dosed until the Investigators have reviewed 72 hours of safety data after dosing the first 2 participants and communicated with the Sponsor Medical Director and Global Medical Safety Physician. Based on this safety evaluation, the Sponsor will determine if the rest of the cohort can be dosed. For the remainder of participants in ~~the~~ **all cohorts, except for** cohort **C2,** no more than 2 participants will receive their first dose of study treatment on the same day throughout the study. **For cohort C2, the participants will be randomized 3:1 (active:placebo). Treatment will be staggered by 72 hours for the first 2 participants. The first 2 participants will be dosed as a sentinel group, and no other participant will be dosed until the Investigators have reviewed safety data after dosing the first 2 participants and communicated with the Sponsor Medical Director and Global Medical Safety Physician. This phone call will occur 72 hours after the dosing of the second participant. Based on this safety evaluation, the Sponsor will determine if the rest of the cohort can be dosed. If approved, the third and fourth participants may receive their first dose of study treatment on the same day**.

For each participant, a review of all available safety and tolerability data will be performed approximately 7 days after the first dose is administered and before administration of the second dose on Day 15. This single-dose review will be performed by the site's Principal Investigator or designee and communicated to the Sponsor Medical Director and Global Medical Safety Physician, or their appropriate designees. The Sponsor Medical Director and Safety Physician will determine if each participant can proceed with subsequent doses. The second dose cannot be administered until this review is complete.

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Rationale: Cohort C2 is designed to enroll 4 participants with polyQ-ALS who will be randomized 3:1 (BIIB105:placebo). To maintain the blinding of the treatment assignment, the sentinel pair for cohort C2 will not be randomized 1:1 (BIIB105:placebo) but instead will be randomly assigned drug or placebo with a minimum of 1 participant receiving drug. To maintain all safety features of the sentinel pair without unblinding, the C2 sentinel pair will have 72 hours between their first doses as described in section 5.1, Study Overview.

This change also affects Section 1.1, Synopsis and Section 3.1, Study Rationale.

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SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 1.1, Synopsis

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

1.3, Schedule of Activities

Change: The Note associated with the C-SSRS Questionnaire was corrected to indicate that the "since last visit" version of the C-SSRS should be used from Day 8 forward, as indicated in the corresponding row in the Schedule of Activities.

Now reads:

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Table 1: Schedule of Activities: Cohorts A, B, C1, C2, and D1

	Screening	Dose 1 (Inpatient)			CV	Dose 2	TC	CV	Dose 3	TC	CV	TC	Dose 4	TC	CV	TC	Dose 5	TC	CV	TC	Follow-Up Period			UV	Notes
Days / **Assessments**	**-28 to -1**	**1**		**2**	**8 (±2)**	**15 (±3)**	**16 (+1)**	**22 (±3)**	**29 (±3)**	**30 (+1)**	**36 (±3)**	**50 (±3)**	**57 (±3)**	**58 (+1)**	**64 (±3)**	**78 (±3)**	**85 (±3)**	**86 (+1)**	**92 (±3)**	**93 (+1)**	**130 (±3)**	**131 (+1)**	**175 (±3)**		Screening assessments can be performed on multiple days (up to 7 days) for ease of participant burden.
		Predose	**Dosing/ Postdose**	**(24 ±1 h) postdose**																					
C-SSRS Questionnaire		X			X	X		X	X		X		X		X		X		X		X		X	X	Use “Since Last Visit” version of C-SSRS from Day ~~15~~**58** onward. Done predose on dosing days. At UV may be assessed per the Investigator’s discretion.

[…]

Table 2: Schedule of Activities: Cohort D2

[…]

[16]Use “Since Last Visit” version of C-SSRS from Day ~~15~~**58** onward. Done predose on dosing days. At UV, may be assessed per the Investigator’s discretion.

Rationale: The Note in Table 1 and the footnote in Table 2 were corrected to fix a discrepancy in the protocol between the Schedule of Activities row indicating the schedule of C-SSRS questionnaire completion and the Note and footnote indicating when the "since last visit" version of the questionnaire should be used.

This change also affects Section 9.1, Clinical Assessments.

6.2, Exclusion Criteria

Change: The definition of the ALSFRS-R slope calculation was corrected.

Now reads:

19. Prescreening ALSFRS-R slope > -0.4 points/month, where prescreening ALSFRS-R slope is defined as follows: (~~48~~**-** ALSFRS-R score at Screening **- 48**) / (months from date of symptom onset to date of Screening) in participants from Cohorts A, B, C1, and D1.

Rationale: The order of the components in the equation to calculate the ALSFRS-R slope at prescreening was incorrect. The change provides clarification in the protocol to ensure correct calculation of the ALSFRS-R slope when determining participant eligibility for the trial.

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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 Page was updated.
- The sentence describing the option to extend the screening period to 42 days for eligible participants was added to Section 6.3.1, Screening. This addition was made to clarify that this extension does not only apply to instances of retesting participants who have a nonclinically significant out-of-range laboratory result.
- Section 6.3.2, Retesting was revised to clarify that the screening period may also be extended to 42 days for retesting of genetic sequencing results.
- Typographical errors and formatting were corrected.

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LIST OF ABBREVIATIONS

ALS	amyotrophic lateral sclerosis
ASLFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised
C-SSRS	Columbia Suicide Severity Rating Scale
CV	clinic visit
ET	early termination
MAD	multiple-ascending dose
polyQ	polyglutamine
TC	telephone contact
UV	Unscheduled Visit

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