COVER PAGE

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:	Part 1 Statistical Analysis Plan: 16 April 2024 Part 2 Final, Integrated Parts 1 and 2: 05 September 2024

STATISTICAL ANALYSIS PLAN

Version No.: Final 1.0

Date: 16 April 2024

Author<s>: [redacted]

Study 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***

Name of Study Treatment: BIIB105

Protocol No.: 275AS01 (Part 1)

Study Phase: 1/2

APPROVAL

This document has been reviewed and approved by:		
[redacted] SMT Statistician	Signature	Date
[redacted], Biostatistics	Signature	Date
[redacted] Medical Director, [redacted]	Signature	Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0	16 April 2024	Not Applicable

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALS	amyotrophic lateral sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
ANCOVA	analysis of covariance
APTT	Activated partial thromboplastin time
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
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	clinic visit
ECG	electrocardiogram
[redacted]	[redacted]
ET	early termination
FAS	full analysis set
[redacted]	[redacted]
INR	international normalized ratio

[redacted]	[redacted]
IQR	Interquartile Range
IRT	interactive response technology
IT	intrathecal(ly)
ITT	Intent-to-treat
LP	lumbar puncture
LS	least square
MAD	multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MMSE	Mini-Mental State Examination
ND	not detectable
NfL	neurofilament light chain
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
[redacted]	[redacted]
PT	prothrombin time
QNS	quantity not sufficient
QTc	Interval between the start of the QRS complex and the end of the T wave, corrected for heart rate
QTcB	QTc interval using Bazett's formula
QTcF	QTc interval using Fridericia's formula
[redacted]	[redacted]
SAE	serious adverse event

SAP	Statistical analysis plan
[redacted]	[redacted]
$t_{½}$	elimination half-life
TC	telephone contact
T_{max}	time to reach maximum observed concentration
TNP	test not performed
UV	Unscheduled Visit
[redacted]	[redacted]

1. Introduction

275AS101 is a two part (Part 1 and Part 2) study. Part 1 is a Phase 1/2, randomized, double-blind, placebo-controlled, MAD evaluation of the safety, tolerability, PK, PD, and effect on clinical function of BIIB105.

Part 2 is an open-label extension study to assess the long-term safety, tolerability, pharmacokinetics, pharmacodynamics, and effects on disease progression of BIIB105 administered IT to adults with ALS and polyQ-ALS who complete Part 1 through Week 25.

The purpose of this Statistical Analysis Plan (SAP) is to describe the final statistical analyses of the Part 1 safety, tolerability, PK, PD, and effect on disease progression on BIIB105 up to Week 25 for cohort A (BIIB105 5 mg), cohort B (BIIB105 20 mg), cohort C1(BIIB105 60 mg), cohort C2 (BIIB105 60 mg for polyQ-ALS), cohort D1 (BIIB105 120 mg), and cohort D2 (BIIB105 120 mg for polyQ-ALS).

2. Study Overview

2.1. Study Objectives and Endpoints

Study Primary Objective

The primary objective is to evaluate the safety and tolerability of BIIB105 in participants with ALS or polyQ-ALS.

Study Primary Endpoint

Incidence of AEs and SAEs in Part 1.

Study Secondary Objective

The secondary objectives are to assess the PK profile of BIIB105 in serum and CSF of participants with ALS or polyQ-ALS, and to evaluate the biomarker effect of BIIB105 in participants with ALS or polyQ-ALS.

Study Secondary Endpoints

The secondary endpoints are listed below:

- Serum and CSF concentrations of BIIB105 in Part 1.
- Serum PK parameters in Part 1:
  - AUC_{inf}
  - AUC_{last}
  - C_{max}
  - T_{max}
  - $t_{1/2}$

- Change from baseline in plasma levels of NfL in Part 1.

[redacted]

- Change from baseline in CSF levels of ATXN2 protein in Part 1.

[redacted]

2.2. Study Design

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.

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.

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 Day 175; they will enroll into Part 2 and follow the Part 2 visit schedule.

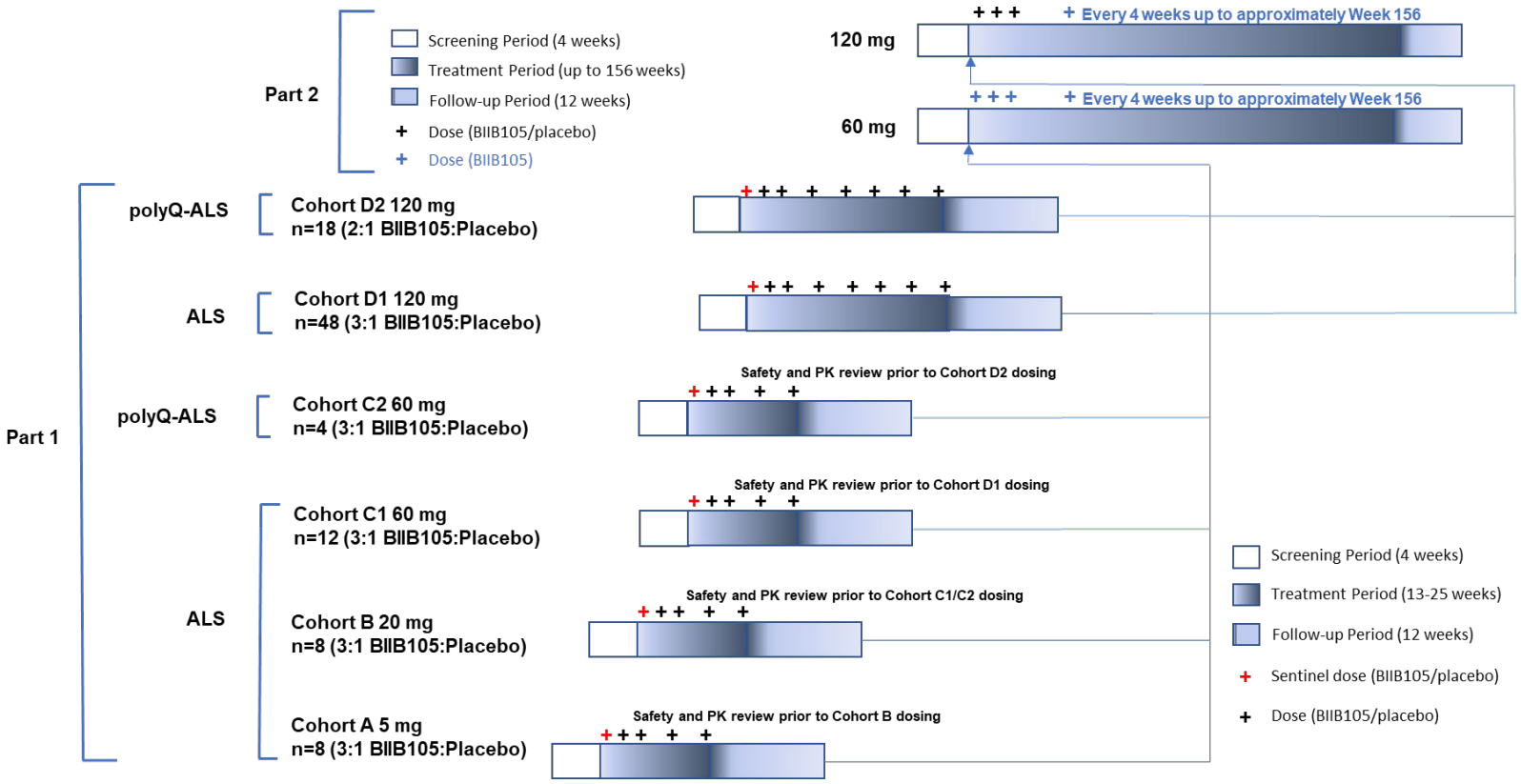
Part 2 is an open-label evaluation of BIIB105 administered IT to participants with ALS and polyQ ALS who have completed Part 1 through Week 25 (Day 175 Visit for Cohorts A, B, C1, C2; Day 176 Visit for Cohorts D1, D2).

Part 2 will not be discussed further in this SAP.

2.2.1. Study Design Schematic

See Figure 1 for a schematic of the study design Schematic.

Figure 1: Study Design



2.2.2. Schedule of Activities

The schedule of activities for Part 1 is presented below.

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

																						Follow-Up Period				
	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		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 (±3)	58 (+1)	64 (±3)	78 (±3)	85 (±3)	86 (+1)	92 (±3)	93 (+1)		130 (±3)	131 (+1)	175 (±3)	176 (+1)	UV
Assessments	-28 to -1	Predose	Dosing/ Postdose	(24 ±1 h) postdose																						
ICF (Main)	X																									
ICF (Informant/ Caregiver)[2]	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																									

Assessments / Days	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
	-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)	CV	TC	Final/ ET Visit	176 (+1)	
		Predose	Dosing/ Postdose	(24 ±1 h) postdose																					
Clinical Laboratory Samples for Viral Serology[3]	X																								
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																								

	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	
Days / Assessments	-28 to -1	1 Predose	1 Dosing/ Postdose	2 (24 ±1 h) postdose	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)	CV 130 (±3)	TC 131 (+1)	Final/ ET Visit 175 (±3)	TC 176 (+1)	UV
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
[redacted]																									
Randomization/ Admission to Inpatient Facility		X																							
Study Treatment Administration[12]			X			X			X				X				X								

Assessments / Days	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
		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)	CV	TC	Final/ ET Visit	176 (+1)	
	-28 to -1	Predose	Dosing/ Postdose	(24 ±1 h) postdose																					
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		
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																					

	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	
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)	UV
Assessments	-28 to -1	Predose	Dosing/ Postdose	(24 ±1 h) postdose																					
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.
[redacted]
[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.

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																								
Clinical Laboratory Samples for Viral Serology[7]	X																								
Serum Pregnancy Test[8]	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]				
																						CV	TC	Final/ ET Visit	TC	UV
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																					
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		
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]				
																						CV	TC	Final/ ET Visit	TC	UV
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																					
[redacted]																									
Participant ventilation diary[19]		X																							
Review ventilation use[20]		X			X	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]				
																						CV	TC	Final/ ET Visit	TC	UV
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																					
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
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		

	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	UV
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																					
[redacted]																									
CSF Sampling[29]		X				X			X				X				X		X[30]		X		X		
Discharge From Inpatient Facility				X																					
Concomitant Therapy and Procedures Recording		X												X											
AE Recording		X												X											
SAE Reporting		X												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.
[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] may be collected up to 24 hours prior to dosing.

[redacted]

[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]
[27] On Day 85 Visit only.
[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.

2.3. Sample Size Considerations

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.

Assuming approximately [redacted]% drop out rate, the combined sample size of Cohorts D1 and D2 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 pooled Cohorts D1 and D2 120 mg data (N=39) vs pooled placebo data across all cohorts (N=23), with a 1-sided [redacted]% significance level, assuming [redacted]% SD in both groups.

3. Definitions

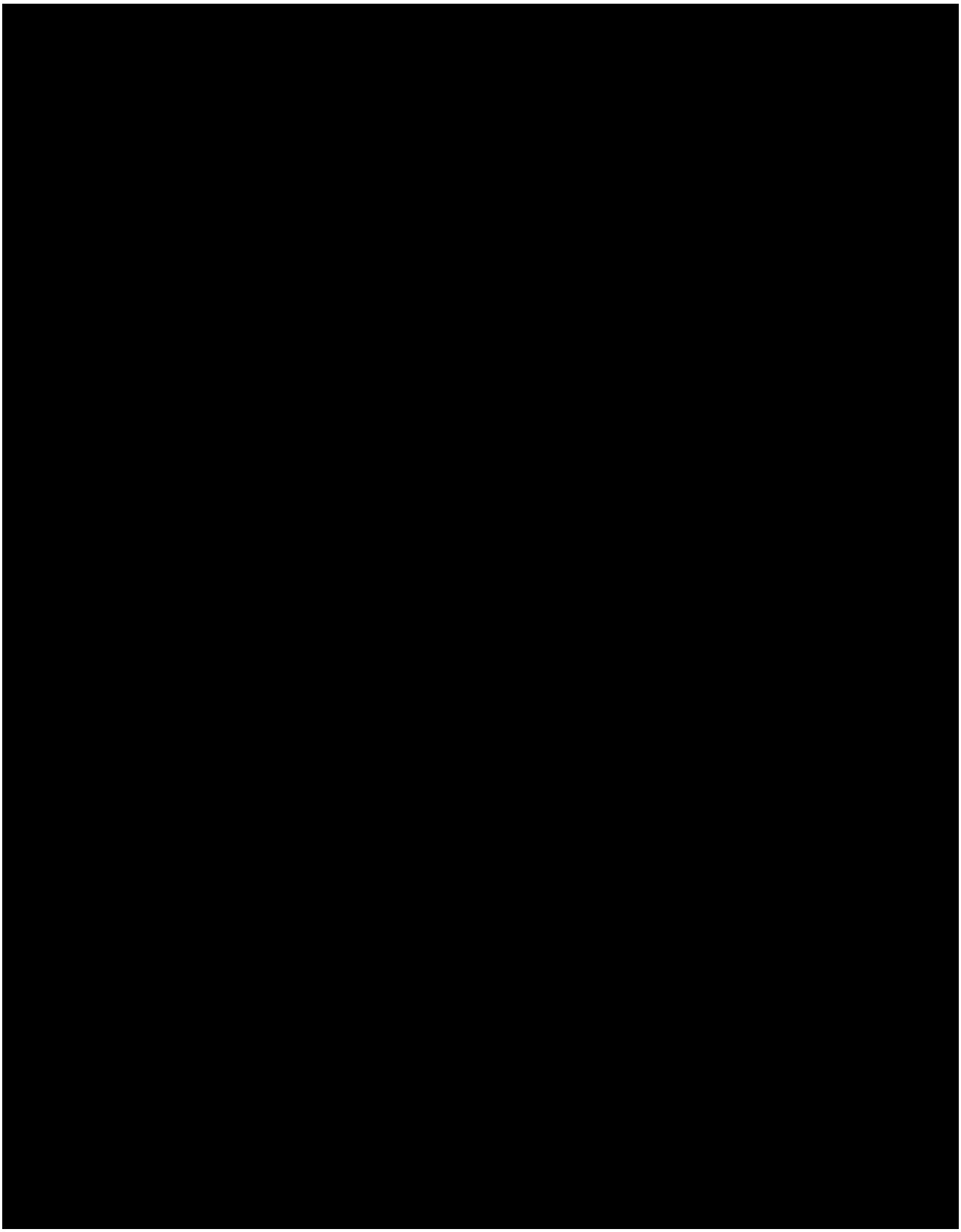
3.1. Dates and Points of Reference

- Study Day 1: the date of the first dose of study treatment
- Study Day
  - For a date on or after Study Day 1
    Study Day = (Date of Interest) – (Study Day 1) +1
  - For a date before Study Day 1
    Study Day = (Date of Interest) – (Study Day 1)
- Baseline: Unless stated otherwise, baseline data are defined as the last data collected prior to the time and/or on the date of first dose, which is usually the same day as the Day 1 Predose/Baseline Visit. If baseline data at Day 1 predose/Baseline visit are missing, the last non-missing data prior to dosing (including data from Screening) will be used as baseline. For PD biomarkers, if predose baseline data (Day 1 predose/baseline or screening data prior to dosing) are missing, the non-missing data collected within 24 hours after first dosing will be used as baseline.
- Data from Assessments at Early Terminated Visit and Unscheduled Visits:

Data from early termination visits and unscheduled visits will be assigned to an appropriate scheduled postbaseline visit using a windowing scheme for assessments that are tabulated or summarized by visit. Scheduled visits will not be windowed. For [redacted] PD biomarkers, the analysis window will be defined based on the schematic as follows:

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 8 Analysis Visit Windows for CSF PK/PD data

Visit	Lower Bound (inclusive)	Upper Bound (inclusive)	Target Day	Cohort
Baseline[(a)]	Last record prior to dosing	Last record prior to dosing	1	All cohorts
Day 15[(a)]	9	22	15	All cohorts
Day 29[(a)]	23	43	29	All cohorts
Day 57[(a)]	44	71	57	All cohorts

Day 85[(a)]	72	88	85	Cohorts A, B, C1, C2 only
Day 85[(a)]	72	99	85	Cohorts D1, D2 only
Day 92	89	111	92	Cohorts A, B, C1, C2 only
Day 113	100	127	113	Cohorts D1, D2 only
Day 130	112	152	130	Cohorts A, B, C1, C2 only
Day 141	128	155	141	Cohorts D1, D2 only
Day 169	156	183	169	Cohorts D1, D2 participants who are dosed in Part 2 after Part 1 treatment period
Day 169	156	172	169	Cohorts D1, D2 participants who are not dosed in Part 2 after Part 1 treatment period
Day 175	153	189	175	Cohorts A, B, C1, C2 only
Day 176	173	195	176	Cohorts D1, D2 participants who are not dosed in Part 2 after Part 1 treatment period
Day 214	196	236	214	Cohorts D1, D2 participants who are not dosed in Part 2 after Part 1 treatment period
Day 259	237	273	259	Cohorts D1, D2 participants who are not dosed in Part 2 after Part 1 treatment period

Note: The lower bounds of visits are calculated as: target day - (target day−target day of previous visit)/2+1. The upper bounds of all visits are calculated as: target day + (target day of next visit – target day)/2 except for Day 175 for cohorts A, B, C1, and C2, which is calculated as: target day + 14, for Day 169 for cohorts D1, D2 participants who are dosed in Part 2 after Part 1 treatment period, and for Day 259 for cohorts D1, D2 participants who are not dosed in Part 2 after Part 1 treatment period, which is calculated as: target day + 14. Both lower and upper bounds are based on all cohort schedules.

(e) Common visits between Cohorts A, B, C1, C2, D1, and D2.

Table 9 Analysis Visit Windows for Plasma PD data

Visit	Lower Bound (inclusive)	Upper Bound (inclusive)	Target Day	Cohort
Baseline(a)	Last record prior to dosing	Last record prior to dosing	1	All cohorts
Day 29(a)	16	43	29	All cohorts
Day 57(a)	44	71	57	All cohorts
Day 85(a)	72	107	85	Cohorts A, B, C1, C2 only
Day 85(a)	72	99	85	Cohorts D1, D2 only
Day 113	100	127	113	Cohorts D1, D2 only
Day 130	108	152	130	Cohorts A, B, C1, C2 only
Day 141	128	155	141	Cohorts D1, D2 only
Day 169	156	183	169	Cohorts D1, D2 participants who are dosed in Part 2 after Part 1 treatment period
Day 169	156	191	169	Cohorts D1, D2 participants who are not dosed in Part 2 after Part 1 treatment period

Day 175	153	189	175	Cohorts A, B, C1, C2 only
Day 214	192	236	214	Cohorts D1, D2 participants who are not dosed in Part 2 after Part 1 treatment period
Day 259	237	273	259	Cohorts D1, D2 participants who are not dosed in Part 2 after Part 1 treatment period

Note: The lower bounds of visits are calculated as: target day - (target day−target day of previous visit)/2+1. The upper bounds of all visits are calculated as: target day + (target day of next visit – target day)/2 except for Day 175 for cohorts A, B, C1, and C2, which is calculated as: target day + 14, for Day 169 for cohorts D1, D2 participants who are dosed in Part 2 after Part 1 treatment period, and for Day 259 for cohorts D1, D2 participants who are not dosed in Part 2 after Part 1 treatment period, which is calculated as: target day + 14. Both lower and upper bounds are based on all cohort schedules.

(f) Common visits between Cohorts A, B, C1, C2, D1, and D2.

Table 10 Analysis Visit Windows for MMSE

Visit	**Lower Bound (inclusive)**	**Upper Bound (inclusive)**	**Target Day**	**Cohort**
Baseline(a)	Last record prior to dosing	Last record prior to dosing	1	All cohorts
Day 8(a)	5	18	8	All cohorts
Day 29(a)	19	43	29	All cohorts
Day 57(a)	44	71	57	All cohorts
Day 85(a)	72	99	85	All cohorts
Day 113	100	127	113	Cohorts D1, D2 only
Day 141	128	155	141	Cohorts D1, D2 only

Day 169	156	183	169	Cohorts D1, D2 only

Note: The lower bounds of visits are calculated as: target day - (target day−target day of previous visit)/2+1. The upper bounds of all visits are calculated as: target day + (target day of next visit – target day)/2 except for Day 175 for cohorts A, B, C1, and C2, which is calculated as: target day + 14, for Day 169 for cohorts D1, D2 participants, which is calculated as: target day + 14. Both lower and upper bounds are based on all cohort schedules.

(a) Common visits between Cohorts A, B, C1, C2, D1, and D2.

If more than one observation is within the same window, data from the regular scheduled visit will be used for that visit.

If neither of the observations are from a regular scheduled visit the observation closest to the target day will be used. However, if both the observations are equally distant from the target day, the latest one will be used if applicable or the average of both observations will be used; if repeated measurements are on the same day, then the last measurement will be used.

Mapping visits may be handled case by case as well, if appropriate.

Early termination visits and unscheduled visits for safety data will be mapped in a similar way.

Some of the safety assessments are collected postdose in addition to the predose assessments (e.g. Neurological Examination at dosing visits, ECG, Vital Signs at Day1 visit, Serum PK at dosing visits). When windowing any predose assessments these should be the last available assessment prior to the dose. When windowing any postdose assessment they should correspond to the same dose as the predose assessment used for that visit. These summaries will present predose and postdose separately on by-visit summaries. If one of these assessments is collected at an unscheduled visit where there is no dosing, the assessment will be assigned as a predose assessment.

Descriptive statistics by visit for vital sign, ECG, Neurological examinations, lab and PK data will be summarized based on scheduled visits once unscheduled and early withdrawal visits are handled as mentioned above. All the postbaseline values will be used from both scheduled and unscheduled visits.

Unless being mapped to missing scheduled visits or specified, the assessments at unscheduled visits will not be used in the summary statistics but will be listed.

3.2. Study Treatment

Participants with ALS:

Cohort A: BIIB105 5 mg or placebo

Cohort B: BIIB105 20 mg or placebo

Cohort C1: BIIB105 60 mg or placebo

Cohort D1: BIIB105 120 mg or placebo

Participants with polyQ-ALS:

Cohort C2: BIIB105 60 mg or placebo

Cohort D2: BIIB105 120 mg or placebo

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.

3.3. Subgroup Variable

Subgroup analyses for selected endpoints may be performed by median baseline NfL level (median across FAS population).

Subgroup analyses for selected endpoints may also be performed based on genetic testing results (including, but not limited to, based on number of ATXN2 polyQ repeats, presence/absence of pathogenic/likely pathogenic mutations in SOD1, FUS, or TDP43 genes, by presence/absence of pathogenic expansions in the C9orf72 gene, or by number of risk alleles on the UNC13A gene).

3.4. Analysis Sets

1) FAS (Full Analysis Set) Population

The FAS population is defined as all randomized participants who received at least 1 dose of study treatment. 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.

2) Safety Analysis Population

The safety analysis population is defined as all randomized participants who received at least 1 dose of study treatment. In the case of any participants who are mis-randomized, then any analyses based on the safety analysis population will be based on actual treatment received.

3) PK Analysis Population

The 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.

4) PD Population

The PD population is defined as participants 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.

[redacted]

4. List of Planned Study Analyses

4.1. Interim Analysis

There is no planned interim analysis for Part 1. However, as the data for Part 1 and Part 2 are in the same database, this is considered an interim lock.

Interim analysis of key safety, secondary, and [redacted] endpoints (including PK, PD, [redacted]) for Part 2 and integrated analyses based on unblinded data from Part 1 and interim data from Part 2 may be conducted; these will be discussed in a separate SAP.

The list of unblinding personnel and details of the unblinding procedure are provided in the 275AS101 Unblinding Plan. The study statistical programmers and biostatisticians will be unblinded following the interim lock. The BIIB105 275AS101 unblinded study team is listed in the Unblinding Plan. Participants, investigators and site staff and sponsor staff responsible for site monitoring and data management will remain blinded to Part 1 treatment assignments until Part 2 completes.

4.2. Primary Analysis

The primary analysis will be conducted after completion of Part 1 Day 175/176 visit for all cohorts (Cohorts A, B, C1, C2, D1, and D2).

4.3. End of Long-term Follow-up Analysis

At the end of the open-label extension of the study (Part 2), to assess long-term safety and efficacy, analysis of safety, secondary, [redacted] endpoints (including PK, PD, clinical function) for Part 2 and integrated analysis of Part 1 and Part 2 will be conducted.

This SAP will only cover the primary analysis for Part 1 once Part 1 Day 175/176 visit has been completed for all cohorts. A separate SAP will detail the integrated analysis.

5. Statistical Methods for Planned Analyses

5.1. General Principles

Descriptive summary statistics will be presented for all primary, secondary, [redacted] endpoints collected. Unless otherwise specified, for continuous endpoints, the summary

statistics will generally include number of participants with data, mean, standard deviation, median, first and third quantiles and range. For categorical endpoints, the summary statistics will generally include number of participants with data, frequency counts and the percentage of those with data in each category.

Analyses will be performed on the data from Part 1 alone.

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

As a general rule, any visit/dose group combination that only has data for 1 participant will not be presented in group plots. All data will be listed, unless otherwise specified.

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

5.2. Participant Accountability

The summaries will be presented by dose level and treatment assignment (BIIB105 5 mg [Cohort A], 20 mg [Cohort B], 60 mg [Cohorts C1+ C2], 120 mg [Cohorts D1+D2], Pooled Placebo 1+Pooled Placebo 2). Selected summaries will also 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), and for all participants.

The number (and percentage) of participants randomized; dosed; completed the treatment; completed Part 1; completed Part 1 treatment period but missed one or more doses; discontinued treatment and the reasons for discontinuation; and withdrew from Part 1 early and the reasons for withdrawal will be summarized in a table. The number of participants who enrolled and completed Part 1 will be summarized. The number of participants who completed up to Part 1 Day 175/176 visit will be summarized. The number (and percentage) of participants who enrolled in Part 2 will also be summarized.

A listing of participants who discontinued treatment/withdrew from Part 1 and the associated reasons for discontinuation/withdrawal will be presented.

The number (and percentage) of participants by analysis population will be summarized.

5.3. Demographic and Baseline Disease Characteristics

All demographics and baseline disease characteristics will be summarized for the FAS population.

Demographic data, including age (years), age category (18-<35, 35-<50, 50-<65, 65-<80, >=80), gender, ethnicity, race, height, weight, and BMI will be summarized by treatment group and overall.

Baseline ALS disease characteristics will also be summarized. The site of onset, form of ALS, mutant genes among participants with familial ALS (as reported by the PI on the eCRF), current usage status of riluzole and edaravone (Yes or No) and their usage duration (< 30 or ≥ 30 days for riluzole and < 60 or ≥ 60 days for edaravone) and [redacted] pre-

screening slope will be summarized as continuous variables. The duration of ALS symptom onset, duration of ALS diagnosis prior to first dosing, baseline [redacted], baseline percent predicted [redacted], and baseline plasma NfL and [redacted] will be summarized as numeric variables with mean, standard deviation (SD), median, first and third quartiles and the range summarized. Geometric mean and geometric CV% will also be summarized for baseline plasma NfL and baseline [redacted]

[redacted]

Genetic data from MNG lab central testing and Biogen internal genetic testing will be integrated and summarized for the FAS population. If the FAS population is different to safety population or clinical function population, summaries will also be presented for these populations. [redacted], SOD1 (presence of pathogenic/likely pathogenic variant Yes or No), FUS (presence of pathogenic/likely pathogenic variant Yes or No), TDP43 (presence of pathogenic/likely pathogenic variant Yes or No), C9orf72 (harbor a pathogenic C9orf72 expansion in at least one allele Yes or No), and UNC13A (number of risk alleles on rs12973192 and rs12608932: 0, 1, or 2).

Additionally, listing of ALS history will be presented along with baseline NfL value, baseline [redacted]

Medical history will be classified using MedDRA version 26.1 or later if available. A summary of medical history by system organ class and preferred term will also be provided for the safety population.

5.4. Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a protocol deviation log. All protocol deviations will be listed and a summary of major protocol deviations by dose group will also be provided. A listing of participants with protocol deviations due to COVID-19 will be provided if any.

5.5. Study Treatment Exposure and Concomitant Medications

Extent of exposure to study treatment will be summarized for the FAS population, by treatment group and overall. If FAS population is different to safety population, summaries will also be presented for safety population.

Number of participants who received BIIB105 or placebo will be summarized by dose group, as well total cumulative dose in mg.

Study drug compliance percentage up to the last dose of study drug received in Part 1 will be defined as the number of doses actually received divided by the number of doses that the subject is expected to receive during the Part 1 study period and will be summarized descriptively and categorically (<80%, 80%-90%, 90%-100%). For participants who withdrew from Part 1 early, the number of expected doses is the planned number of doses before the time of withdrawal.

Separate listings will be provided showing what participants were randomized to as well as study drug administration which will include lot numbers.

Duration of exposure and time on study will be summarized descriptively by dose group. Duration of exposure will be calculated as (last dose date – first dose date +1) in days and time on study will be calculated as (end of study date – first dose date +1) in days.

Concomitant medications will be coded using the World Health Organization (WHO) dictionary WHODRUG (Sep 2023) and concomitant non-drug treatments/procedures using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 or later if available.

Medications and non-drug treatments are considered concomitant if they are taken during the study. This includes medications/treatment/procedures that were started prior to the date and time of first dose of study drug if their use continued on or after the date and time of first dosing. If the start date is available but start time is missing and the medication/non-drug treatment start date is the same as the first dose date, the medication/non-drug treatment will be considered concomitant. Similarly, if the stop date is available but stop time is missing and the medication/non-drug treatment stop date is the same as the first dose date, the medication/non-drug treatment will also be considered concomitant. Medications/therapies with missing start or stop dates and times, will also be considered as concomitant in the following situations:

- If both the start and stop dates and times of a medication/treatment/procedure are missing.
- If the start date and time of a medication/treatment/procedure is missing and the stop date and time of the medication/therapy occurred on or after the date and time of first dose of study drug.
- If the start date and time of a medication/treatment/procedure therapy occurred prior to the date and time of first dose of study drug and the stop date and time of the medication/treatment/procedure is missing and the medication/treatment/procedure is listed as ongoing.

If the start date and time of a medication/treatment/procedure occurred prior to the date and time of first dose of study drug and the stop date and time of the medication/treatment/procedure is missing and the medication/therapy is not listed as ongoing, then the medication/treatment/procedure will be considered as concomitant.

The number and percentage of participants taking any concomitant medications will be summarized for the safety population. The number and percentage of participants taking any concomitant non-drug treatments will also be summarized for the safety population.

[redacted]

[redacted]

[redacted]

For each of the 100 imputed datasets, change from baseline will be calculated using the imputed datasets, and the change from baseline endpoint will be compared between treatment groups (BIIB105 60 mg vs Pooled Placebo 1+2 and BIIB105 120 mg vs Pooled Placebo 1+2) using an ANCOVA model for continuous endpoints ([redacted] and pharmacodynamic endpoints). The ANCOVA model will include covariates for each of the corresponding baseline value for the endpoint, baseline plasma NfL, [redacted] The model will be used to present overall LS means and standard errors for each treatment group (Pooled Placebo 1+2, BIIB105 60 mg and BIIB105 120 mg), and LS mean differences for treatment (BIIB105 60 mg vs Pooled Placebo 1+2 and BIIB105 120 mg vs Pooled Placebo 1+2) with corresponding 95% CI and p-values. A combined estimate of the LS means, LS mean differences and standard errors of the 100 imputed datasets will be obtained, where standard errors will be used to obtain 95% CI from PROC MIANALYZE [Little et al, 2002]. Separate ANCOVA models will be used to obtain estimates, 95% confidence intervals and p-values for other visits. [redacted]

For analyses of Part 1, ANCOVA model will be performed to compare BIIB105 60 mg vs. Pooled Placebo 1+2 and BIIB105 120mg vs. Pooled Placebo 1+2.

As scheduled visits are different between cohorts A, B, C1, C2 and cohorts D1, D2, scheduled visits from cohorts A, B, C1, C2 might be combined with selected scheduled visits from cohorts D1, D2 when placebo participants from different cohorts are pooled to perform descriptive analysis, multiple imputation and ANCOVA.

Table 12 Scheduled Visits from Different Cohorts – Part 1

Endpoints	Scheduled Visits Cohort A, B, C1, C2	Scheduled Visits Cohort D1, D2	Visits Combination
[redacted]			
PD biomarkers	Baseline, 29, 57, 85, 130, 175	Baseline, 29, 57, 85, 113, 141, 169	Day 130/141, Day 169/175

[redacted]

5.6.2. ALSFRS-R

General Description

The ALSFRS-R is a questionnaire to measure degree of impairment in 4 functional domains: respiratory function, bulbar function, gross motor skills, and fine motor skills. Each domain consists of 3 items, each scored from 0 to 4, with higher scores representing better function. Each domain can have maximum score of 12 and the total possible score for ALSFRS-R is 48. The items for each domain are listed below.

- Respiratory function: dyspnea, orthopnea and respiratory insufficiency
- Bulbar function: speech, salivation and swallowing
- Gross motor skills: turning in bed, walking and climbing Stairs
- Fine motor skills: handwriting, cut and handling utensils without or with gastrostomy, dressing and hygiene

[redacted]

[redacted]

5.6.3. HHD Megascore

General Description

Twenty-two muscles in 11 pairs are examined in both upper and lower extremities (left and right shoulder flexion, left and right elbow flexion, left and right elbow extension, left and right wrist extension, left and right abduction index finger, left and right abduction thumb, left and right abduction 5th digit, left and right hip flexion, left and right knee flexion, left and right knee extension, left and right ankle dorsiflexion).

Each muscle is tested at least twice. If the difference between the first two trials is greater than 15%, or if the evaluator thinks that one of the first two trials was not valid, a third trial may be performed. The maximum value of the two highest measures within 15% variability will be used for the analysis. If there is no pair with ≤15% variability, then the maximum value of the two values that are closest together will be used for the analysis.

[redacted]

5.6.4. Percent Predicted SVC

General Description

Vital capacity will be measured by means of the slow vital capacity (SVC) test using a facemask with the participant sitting upright. SVC will be determined by performing at least 3 trials. If the difference between the two highest values of the three trials is ≥10%, then up to 5 trials may be performed. The maximum percent predicted SVC value at each visit will be used for the analysis.

[redacted]

[redacted]

5.7. Safety Endpoints

The safety population will be used for the analyses of the safety data. Safety data will be summarized using descriptive statistics by dose level or cohort.

All adverse events (AEs) and serious adverse events (SAEs), clinical laboratory data, vital sign measurements, neurological exams, ECG readings, and CSSRS will be evaluated for safety. Safety data will be summarized using descriptive statistics.

Safety data will be summarized by dose level and treatment assignments (BIIB105 5 mg [Cohort A], 20 mg [Cohort B], 60 mg [Cohorts C1+ C2], 120 mg [Cohorts D1+D2], Pooled Placebo 1+2. Selected safety data will also 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).

5.7.1. Adverse Events

All AEs will be classified using MedDRA version 26.1 or later if available. Only treatment emergent AEs (TEAEs) will be summarized, where treatment emergence will be relative to the first dose of study drug. A treatment emergent AE/SAE is defined as any AE/SAE with an onset date that is on or after the first dose of study drug or any pre-existing condition that has worsened in severity after the first dose of study drug. Whenever possible, date/time will be used to determine whether an event is treatment emergent. If an event date (start or end) is incomplete, a TEAE will be determined assuming most conservate way as follows:

- If onset day is missing and the month and year are the same as or after the treatment start date, then that event is considered treatment emergent.
- If both onset month and day are missing and the year is the same as or after the treatment start date, then that event is considered treatment emergent.
- If both onset date and end date are completely missing, an event will be considered as a TEAE.
- If onset date is completely missing and end date is not missing which is after the first dose of study drug, an event will be considered as a TEAE.

The incidence of TEAEs will be summarized by dose level (or cohort) and overall BIIB105 as follows:

- Overall summary of TEAE
- TEAEs by primary SOC and MedDRA preferred term
- TEAEs by MedDRA preferred term
- SAEs by primary SOC and MedDRA preferred term
- SAEs by MedDRA preferred term
- Related SAEs by primary SOC and MedDRA preferred term
- TEAEs by CTCAE grading, primary SOC and MedDRA preferred term
- TEAEs with severity greater than or equal to 3 by primary SOC and MedDRA preferred term
- Related TEAEs by primary SOC and MedDRA preferred term
- TEAEs that led to discontinuation of study treatment by primary SOC and MedDRA preferred term
- TEAEs that led to study drug interruption by primary SOC and MedDRA preferred term

- TEAEs that led to withdrawal from study by primary SOC and MedDRA preferred term
- TEAEs related to the lumbar puncture by primary SOC and MedDRA preferred term
- TEAEs that led to death by primary SOC and MedDRA preferred term
- TEAEs within 24 hours of dosing by primary SOC and MedDRA preferred term

Due to the different durations of exposure to BIIB105 and washout periods for some participants, exposure-adjusted incidence rates will be summarized. Follow-up adjusted incidence rates will also be summarized.

For the summary of TEAEs by severity, primary system organ class and/or preferred term, participants will be counted only once within each primary SOC/MedDRA preferred term and will only be counted under the maximum severity.

For the summary of TEAEs by relationship to study treatment, a subject will be counted only once and in the category of the strongest relationship to study treatment within each SOC/preferred term. The relationship to study treatment will be classified as related or not related.

Listings of all AEs, SAEs, AEs that led to study drug discontinuations, AEs that led to study withdrawals, and AEs that led to study rug interruption will be presented. Listing of death will be provided.

5.7.2. Laboratory Data

Laboratory data will be evaluated to determine the incidence of abnormalities that emerge during the study. Changes in laboratory evaluations will be presented relative to baseline, which is defined as the closet visit prior to the subject start treatment. Baseline value is defined as data collected which are prior to and/or on the date of the first dose, usually also the same day as the Day 1 visit. If there is more than one value on or before Day 1, then the last non-missing value prior to (including on) the date of first dose will be used as the baseline value.

The following clinical laboratory parameters are assessed in the protocol:

- Hematology panel: complete blood count with differential
- Blood chemistry panel: 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)
- CSF analysis: red blood cell count, white blood cell count, protein, and glucose.
- Coagulation: PT (prothrombin time), aPTT (activated partial thromboplastin time), and INR (international normalized ratio).

Shift analyses

Each hematology, blood chemistry, coagulation and CSF laboratory parameter will be flagged as "low" or "high" relative to the parameter's normal range or as "unknown" if no results is available. All visits with available results, including unscheduled visits, will be included in shift analysis.

For each urinalysis laboratory parameter, the number and percentage of participants experiencing post-dosing shifts to abnormal will be summarized.

For each hematology, blood chemistry, coagulation and CSF laboratory, the number and percentage of participants experiencing post-dosing shifts to "low" or "high" will be summarized. Shift to low includes results from normal to low, high to low, and unknown to low. Shift to high includes results from normal to high, low to high, and unknown to high. In each summary, the denominator for the percentage is the number of participants at risk for the shift. The number at risk for the shift to low is the number of participants whose baseline values is not low and who have at least one post-baseline value. The number at risk for the shift to high is the number of participants whose baseline value is not high and who have at least one post-baseline value. A participant will be counted only once for each parameter and each type of shift if there are more than one occurrence for that parameter and that type of shift among post-dosing assessments. Participants with shift will be listed by laboratory parameter and shift type.

Summary of change from baseline and other analysis

In addition to the shift analysis, descriptive statistics (N, mean, SD, median, 1st and 3rd quartiles, and minimum and maximum values) for observed laboratory values, change from baseline and percentage change from baseline in laboratory values of hematology, blood chemistry, and coagulation will be summarized by treatment group and visit. Line plots showing mean and change from baseline value for each treatment over visits will also be presented. Only scheduled visits will be included in these summaries. Spaghetti plots by site will be presented for CSF samples. Proportion of participants with CSF WBC values above 5, 10, and 20 10^6/L and proportion of participants with CSF protein level above 4X, 3X, and 2X ULN (upper limit of normal) will be summarized.

Listing of all chemistry, hematology, coagulation, CSF, and urinalysis values will be provided. Abnormal values will be flagged.

5.7.3. Vital Signs

Summary statistical for actual values and change from baseline will be presented for each visit and vital sign parameters (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure). Weight will be summarized along with vital signs.

The incidence of clinically significant post baseline abnormalities will be summarized per the criteria below:

- Temperature <36°C or >38°C
- Weight 7% or more increase from baseline; 7% or more decrease from baseline
- Systolic blood pressure <90 mmHg or >140 mmHg or >160 mmHg
- Diastolic blood pressure <50 mmHg or >90 mmHg or >100 mmHg
- Pulse rate <60 beats/minute or >100 beats/minute
- Respiratory rate <12 breaths/min or >20 breaths/min

A listing of vital sign data will be provided.

5.7.4. ECG

Triplicate 12-lead electrocardiograms (ECG) are to be collected at the timepoints specified in Schedule of Activities. The continuous (non-categorical) ECG test measured in triplicate includes heart rate, PR interval, QRS interval, QT interval, QTc interval using Fridericia's formula (QTcF) and RR interval. Each triplicate ECG is also interpreted as "normal", "abnormal" or "not evaluated". The number and percentage of participants with shifts from normal to abnormal will be summarized by treatment group. All postbaseline data will be used to identified abnormalities, regardless of whether a scheduled or unscheduled visit.

The mean of the triplicate continuous ECG parameter values at each nominal timepoint will be used for the analyses. If any triplicate within a nominal timepoint is abnormal, the interpretation will be counted as abnormal once for that nominal timepoint.

Actual values and change from baseline for the continuous (non-categorical) ECG parameters will be descriptively summarized by timepoint. Baseline for these analyses will be the mean of the replicate values from predose Day 1. If there are no replicates for predose Day 1, then the mean of the replicates from Screening will be used.

The number and proportion of participants whose QTcF results or change values meet certain predefined criteria (listed below) will be summarized.

- Absolute QTcF interval > 450 msec
- Absolute QTcF interval > 480 msec
- Absolute QTcF interval > 500 msec
- Changes from baseline QTcF >30 msec
- Changes from baseline QTcF > 60 msec

A listing of both qualitative and quantitative ECG data will be presented.

5.7.5. Neurological Examination

The neurological examinations include cranial nerves, motor, reflexes, cerebellar function, and mental status (MMSE in Part 1).

For cranial nerves/cerebellar function, a frequency table will be created for the tests of nystagmus, gait, and tremor. The number of participants with the outcomes (Absent, Present, or Not Done for the test of nystagmus, gait, and tremor, and Abnormal, Normal, or Not Done for other tests) will be summarized by treatment group and visit.

For reflexes examination, a frequency table will also be created for the tests of Hoffman signs and plantar response. The number of participants with the outcomes (Absent, Present, Not Done for Hoffman signs and Flexor/Extensor/Undetermined for plantar response) will be summarized by treatment group and visit. For other tests, a figure on mean scores (0=Absent, 1=Trace, 2=Normal, 3=Brisk, 4=Non-sustained clonus, 5=Sustained clonus) will be plotted versus visit. In addition, the proportion of participants with hypo-reflexia (scores 0 or 1) or apparent hyper-reflexia (scores of 3 or 4 or 5) will be summarized and the corresponding figure will also be generated.

For motor examination, a figure on mean scores vs. visit will be generated by treatment group.

Summary statistics for actual values and change from baseline of the total score of MMSE will be presented for each visit by treatment group. When there are multiple assessments during a single visit, the minimal value will be taken as the value for that visit. A listing of MMSE data will also be provided.

Neurological examinations will be presented in listings as well.

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

The details of derivation and imputation for C-SSRS is described in Appendix 2. The following analyses on C-SSRS measurements will be conducted.

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

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

5.8. Pharmacokinetic Endpoints

The PK population will be used for the analyses of the PK data.

For the PK analysis, the serum and CSF BIIB105 concentrations will be listed and summary statistics (n, mean, SD, median, range, geometric mean and coefficient variation of geometric mean) will be presented by time for each visit. Plots of arithmetic and geometric mean concentration of serum and CSF BIIB105 versus time will be provided. Values below limit of quantitation (BLQ) prior to first dosing will be set to 0 and other BLQ will be set to half of lower limit of quantitation (LLOQ). The LLOQs are 1 ng/mL and 0.25 ng/mL for serum PK and CSF PK, respectively.

Non-compartmental analyses will be conducted by the Clinical Pharmacology and Pharmacometric group or their designate and the calculated PK parameters will be provided to Biostatistics. Summary statistics (n, mean, SD, CV%, median, range, geometric mean, CV% of geometric mean) will also be provided, if applicable, for serum PK parameters of AUC_{∞}, AUC_{last}, C_{max}, T_{max}, and t1/2 for Days 1, 15, 29, 57, 85 for Cohorts A, B, C1 and C2. The PK parameters for Cohorts D1 and D2 will be estimated for Days 1, 15, 29, 57, 86, 114, 142, and 169. Additional PK parameters may be calculated at the discretion of the Pharmacokinetic scientist. Listing of serum PK parameters will also be generated.

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]).

5.9. Pharmacodynamic Endpoints

General Considerations

The PD population will be used for the analyses of the PD data. The following PD markers and biomarkers will be assessed:

- CSF ATXN2
- Plasma NfL

Other PD markers or biomarkers that may be available will be analyzed similarly to those listed above if appropriate.

BLQ values will be set as half of LLOQ in the analysis, if applicable. ND (not detectable), TNP (test not performed), and QNS (quantity not sufficient) values will be set to missing in the analysis. [redacted] and the LLOQ for plasma NfL is 1.38 pg/mL.

Missing data at each visit will be imputed using multiple imputation.

For analyses of Part 1, data will be analyzed in a similar way as specified for [redacted]

Sensitivity analyses will be performed by excluding potential outliers. All records from subjects whose baseline was identified as outliers will also be excluded from this sensitivity analyses as well.

Descriptive Statistics

Descriptive statistics for each PD biomarker at each visit for observed values and ratio to baseline will be summarized by treatment group. The summary statistics will include arithmetic mean along with SD, 1st and 3rd quartiles, median and range as well as the geometric mean (for observed values) or geometric mean ratio (for ratio to baseline) with the corresponding standard errors. The geometric mean and geometric mean ratio will be obtained by back-transforming means and change from baseline on natural logarithmically transformed data.

Spaghetti plot will be presented by dose level.

In addition to the analyses above the following plots over time will be presented for each biomarker as appropriate:

- Arithmetic mean ratio to baseline with standard error bars
- Geometric mean ratio to baseline with standard error bars

Missing Data

For each of the PD biomarkers, any missing postbaseline will be imputed using multiple imputation (MI). Baseline will not be imputed. The MI model will be performed based on log transformed data for each PD biomarker using the methods described in clinical function section. There will be no resetting of imputed values. The seed used for each PD biomarker is given in Table 12. Before running the model, the dataset will be sorted by cohorts and treatment group and by USUBJID.

Table 13: Seed used for each PD endpoint in MI

Endpoint	Seed
[redacted]	[redacted]
Plasma NfL	3847243

Statistical Analyses

For the statistical analysis of PD biomarkers, the data will be transformed using the natural logarithmic scale.

The following statistical analyses will be evaluated in PD population:

For analyses of Part 1, ANCOVA model will be performed for BIIB105 60 mg vs. Pooled Placebo 1+2 and BIIB105 120 mg vs. Pooled Placebo 1+2.

An ANCOVA model for log ratio to baseline will be performed on change from baseline values on log scale (i.e. log(postbaseline)-log(baseline)) for each of the 100 imputed datasets for each PD biomarker. The model will include covariates for the corresponding baseline value, i.e. log value, baseline disease duration since symptom onset, and use of riluzole or edaravone. The least square (LS), i.e. adjusted mean of each treatment group, as well as the treatment group differences will be presented with 95% confidence intervals (CIs) and the p-value.

The following plots over time will be presented for each PD biomarker using the MI imputed datasets where appropriate:

- Arithmetic mean ratio to baseline with standard error bars
- Geometric mean ratio to baseline with standard error bars

Listing of individual data will also be provided.

[redacted]

[redacted]

[redacted]

[redacted]

6. Changes from Protocol-Specified Analyses

- [redacted]
- [redacted]
- [redacted]
- As we do not expect to see many events during the 6 month period, we remove the time to event analyses since symptom onset.

7. References

Protocol 275AS101 Protocol Version 5.0

275AS101 Unblinding Plan Version x.0

[redacted]

APPENDICES

Appendix 1: Derivation of Demographic and Baseline Characteristics

BMI will be calculated as weight (kg) / height^2 (m^2).

Time since ALS symptom onset will be calculated in months as (date of first dose received – date of ALS symptom onset)/30.4375. Time since ALS diagnosis will be calculated in months as (date of first dose received – date of ALS diagnosis)/30.4375. For the purpose of these calculations partial dates for ALS symptom onset or ALS diagnosis will be imputed as follows: missing day will be imputed with 15th and missing month/day will be imputed with January 15th.

[redacted] Partial dates for symptom onset will be handled as defined above.

Appendix 2: Derivation of C-SSRS

The Columbia Suicide Severity Rating Scale (C-SSRS) is an assessment that evaluates suicidal ideation and behavior. C-SSRS measurements are collected with respect to "Lifetime: time he/she felt most suicidal" at baseline, and with respect to dose day and ET visit.

There are 11 common "Yes/No" questions at baseline and postbaseline visits. Five questions on *suicidal ideation* and five questions on *suicidal behavior* are re-ordered and follow increasing severity order respectively as shown table. In particular, only patients who answered "Yes" to question 2 will proceed to question 3, 4 and 5. Thus, for any participants who answered "No" to question 2, an answer "No" will also be assumed to question 3, 4, and 5. An additional "Yes/No" question is used to record if subject had committed suicide in postbaseline visits.

Table: C-SSRS re-ordered questions

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

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

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

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

[redacted]

[redacted]

STATISTICAL ANALYSIS PLAN

Version No.: Final 1.0

Date: 05 September 2024

Author<s>: [redacted]

Study 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***

Name of Study Treatment: BIIB105

Protocol No.: 275AS01 (Part 2 Final, Integrated Parts 1 and 2)

Study Phase: 1/2

APPROVAL

This document has been reviewed and approved by:		
[redacted] SMT Statistician	Signature	Date
[redacted], Biostatistics	Signature	Date
[redacted] Medical Director, [redacted]	Signature	Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0	September 05 2024	Not Applicable

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALS	amyotrophic lateral sclerosis
[redacted]	[redacted]
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised
ANCOVA	analysis of covariance
APTT	Activated partial thromboplastin time
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	clinic visit
ECG	electrocardiogram
[redacted]	[redacted]
ET	early termination
FAS	full analysis set
HHD	handheld dynamometry
INR	international normalized ratio
[redacted]	[redacted]
IQR	Interquartile Range

IRT	interactive response technology
IT	intrathecal(ly)
ITT	Intent-to-treat
LP	lumbar puncture
LS	least square
MAD	multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MMSE	Mini-Mental State Examination
ND	not detectable
NfL	neurofilament light chain
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	prothrombin time
QNS	quantity not sufficient
QTc	Interval between the start of the QRS complex and the end of the T wave, corrected for heart rate
QTcB	QTc interval using Bazett's formula
QTcF	QTc interval using Fridericia's formula
[redacted]	[redacted]
SAE	serious adverse event
SAP	Statistical analysis plan
SVC	slow vital capacity

TC	telephone contact
TNP	test not performed
UV	Unscheduled Visit
[redacted]	[redacted]

1. Introduction

275AS101 is a two part (Part 1 and Part 2) study. Part 1 is a Phase 1/2, randomized, double-blind, placebo-controlled, MAD evaluation of the safety, tolerability, PK, PD, [redacted] of BIIB105.

Part 2 is an open-label extension study to assess the long-term safety, tolerability, pharmacokinetics, pharmacodynamics, and effects on disease progression of BIIB105 administered IT to adults with ALS and polyQ-ALS who complete Part 1 through Week 25.

The purpose of this final Statistical Analysis Plan (SAP) is to describe in detail the planned statistical analyses on final data from Part 2 and selected integrated data from 275AS101 Part 1 and Part 2 as of the final database lock to support the final clinical study report (CSR).

The study was terminated early by the sponsor based on the results from study 275AS101 Part 1 and integrated interim results from Part 1 and Part 2 which indicated there was no effect in neurofilament and no clinical benefit in patients treated with BIIB105. The statistical analyses are being simplified for an abbreviated CSR due to the early termination of the study.

2. Study Overview

2.1. Study Objectives and Endpoints

The objective of this final analysis is to evaluate the long-term safety and tolerability of BIIB105 in participants with ALS or PolyQ-ALS in Part 2 and integrated Part 1 and Part 2, and to support the final abbreviated CSR. The relevant key endpoints are listed below:

- Incidence of AEs and SAEs
  - Incidence of AEs and SAEs in Part 2
  - Incidence of AEs and SAEs during the BIIB105-treated period (60 mg and 120 mg) in Part 1 and/or Part 2.
- CSF concentrations of BIIB105 120 mg in Part 1 and Part 2.
  - CSF PK concentration
- Changes from Part 1 baseline (Cohorts D1, D2) or Part 2 baseline (Cohorts A, B, C1, C2) in ALSFRS-R
- Changes from Part 1 baseline (Cohorts D1, D2) or Part 2 baseline (Cohorts A, B, C1, C2) in SVC
- Changes from Part 1 baseline (Cohorts D1, D2) or Part 2 baseline (Cohorts A, B, C1, C2) in HHD
- [redacted]
- Survival analyses for BIIB105 120 mg

- 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, permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days), or withdrawal from study due to disease progression.

- [redacted]
  - [redacted]

2.2. Study Design

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.

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.

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 Day 175; they will enroll into Part 2 and follow the Part 2 visit schedule.

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.

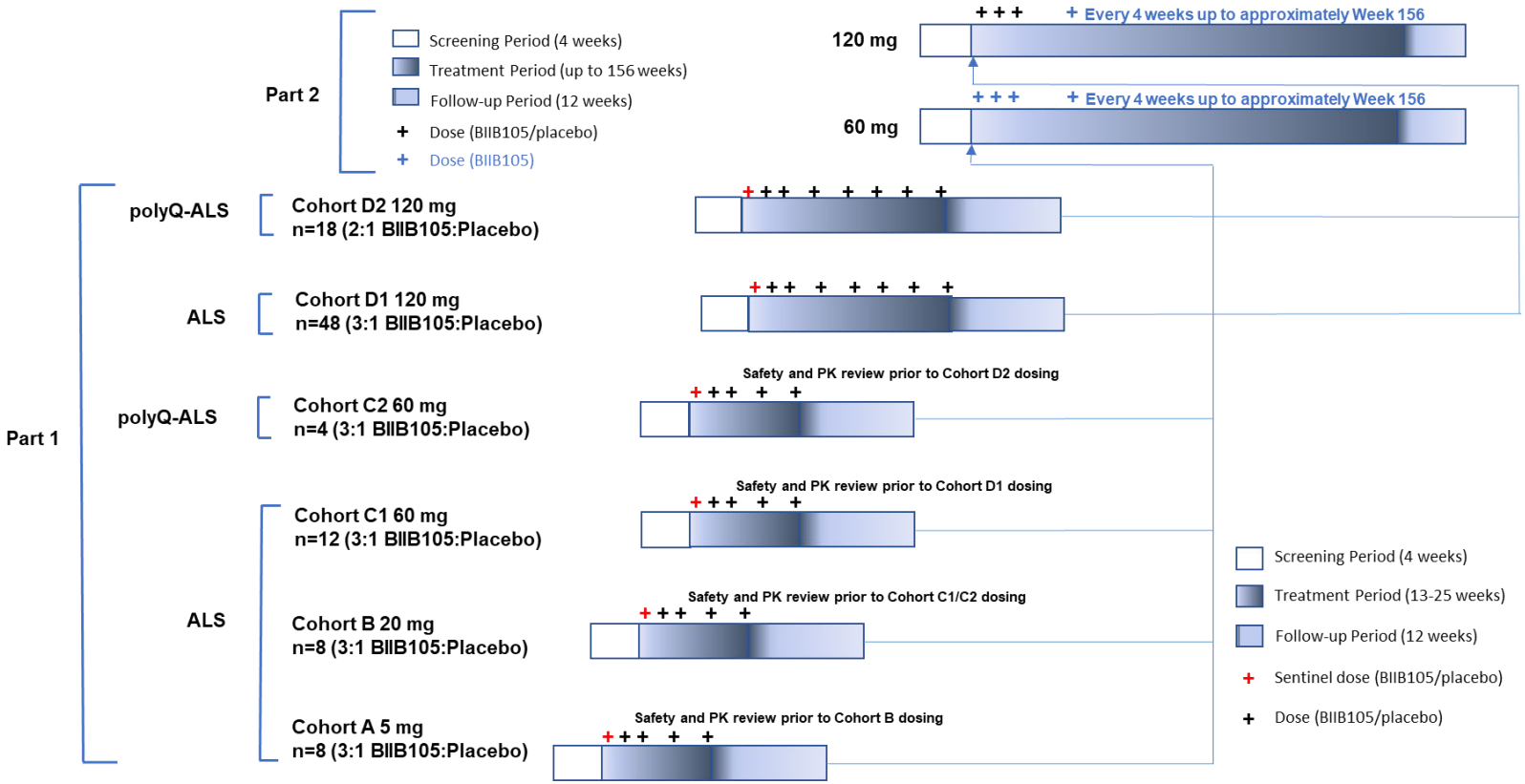
In Part 2, the 60 mg dose may be increased, at the Sponsor's discretion, to doses up to 120 mg. Before increasing the dose level, the SST must review safety and PK data for Cohort D1 and D2 (Part 1) and there must be agreement that the current emerging safety, tolerability, and PK data support the dose increase. The 60 mg dose in Part 2 was increased to 120 mg following the SST review on 13 December 2023.

Doses in Part 2 may also be decreased at the Sponsor's discretion at any time during the study.

2.2.1. Study Design Schematic

See Figure 1 for a schematic of the study design Schematic.

Figure 1: Study Design



2.2.2. Schedule of Activities

The schedule of activities is presented below.

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	
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)	CV 130 (±3)	TC 131 (+1)	Final/ ET Visit 175 (±3)	176 (+1)	UV
Assessments	-28 to -1	Predose	Dosing/ Postdose	(24 ±1 h) postdose																					
ICF (Main)	X																								
ICF (Informant/ Caregiver)[2]	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																								

Assessments / Days	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
	-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)	176 (+1)	
		Predose	Dosing/ Postdose	(24 ±1 h) postdose																					
Clinical Laboratory Samples for Viral Serology[3]	X																								
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																								

	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 / Assessments	-28 to -1	1 Predose	1 Dosing/ Postdose	2 (24 ±1 h) postdose	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)	CV	TC	Final/ ET Visit	176 (+1)	
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		
ALSFRS-R[11]	X	X							X		X		X		X		X		X		X		X		
[redacted]																									
HHD[11]	X								X				X				X		X		X		X		
[redacted]																									
Randomization/ Admission to Inpatient Facility		X																							
Study Treatment Administration[12]			X			X			X				X				X								

Assessments / Days	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
		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)	
	-28 to -1	Predose	Dosing/ Postdose	(24 ±1 h) postdose																			Final/ ET Visit		
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		
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																					

Assessments / Days	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
		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)	
	-28 to -1	Predose	Dosing/ Postdose	(24 ±1 h) postdose																			Final/ ET Visit		
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.

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																								
Clinical Laboratory Samples for Viral Serology[7]	X																								
Serum Pregnancy Test[8]	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 / Assessments[5]	-28 to -1	1 Predose	1 Dosing/Postdose	2 (24 ±1 h) postdose	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]	
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		
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]				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																					
[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]																									
HHD[21]		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
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																					
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
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		

	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																					
Blood Sampling for RNA[21]		X											X[27]				X								
[redacted]																									
CSF Sampling[29]		X				X			X				X				X		X[30]		X		X		
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.
[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]

[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.

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

	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**
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]														

		Loading Dose Period						**Maintenance Dose Period**		**Follow Up Period**				
	Screening[1]	**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]														
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		

	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]														

	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]														
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

	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**
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]						
Blood Sampling for Biomarkers[19]		X				X		X		X		X		
[redacted]														
CSF Sampling[25]		X		X		X		X		X		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**
Concomitant Therapy and Procedures Recording		Ongoing												X
AE Recording		Ongoing												X
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] 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.

2.2.3. 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]%, [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.

Assuming approximately [redacted]% drop out rate, the combined sample size of Cohorts D1 and D2 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 pooled Cohorts D1 and D2 120 mg data (N=39) vs pooled placebo data across all cohorts (N=23), with a 1-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.

3. Definitions

3.1. Dates and Points of Reference

Unless stated otherwise, baseline data for Part 1 and Part 2 are defined as the last data collected prior to the time and/or on the date of first dose in Part 1 or Part 2, which is usually the same day as the Day 1 Predose/Baseline Visit. If baseline data at Day 1 predose/Baseline visit are missing, the last non-missing data prior to dosing (including data from Screening) will be used as baseline. For PD biomarkers, if predose baseline data (Day 1 predose/baseline or screening data prior to dosing) are missing, the non-missing data collected within 24 hours after first dosing will be used as baseline.

[redacted]

For the safety and PK data in the integrated analysis of Part 1 and Part 2, the baseline is defined as the day when the subjects receive their first dose of BIIB105 (60 mg or 120 mg) either in Part 1 or Part 2.

For PD, and efficacy data in the integrated analysis of Part 1 and Part 2, only participants from Part 1 Cohorts D1 and D2 are included. The baseline is defined as the Day 1 of Part 1 for the included subjects from Part 1.

Windowing and mapping will be applied to visits from both Part 1 and Part 2 to obtain analysis visits for the integrated analysis. Study day of a visit is calculated as (visit date – Day 1 or baseline) for a date before baseline, and as (visit date – Day 1 or baseline +1) for a date on or after baseline, respectively.

Only data from post-baseline unscheduled visits and early termination visits will be assigned to appropriate scheduled post-baseline visits using a windowing scheme as specified below by the target, lower, and upper study days. There will be no visit windows applied to scheduled visits. Once these visits have been windowed, a mapping algorithm will be applied to all available visits included for presenting by-visit summaries and analyses since Part 1 baseline.

For ALSFRS-R visits from Part 1 for subjects from Cohorts D1 and D2, for example, we follow the table:

Table 1 Analysis Visit Windows for ALSFRS-R – Part 1 Cohorts D1+D2

Analysis Visit	Visit in Part 1	Target Day	Lower Bound (inclusive)	Upper Bound (inclusive)
Baseline	Day 1	1	Last record prior to dosing	Last record prior to dosing
Week 4	Day 29	29	16	32
Week 5	Day 36	36	33	46
Week 8	Day 57	57	47	60
Week 9	Day 64	64	61	74
Week 12	Day 85	85	75	88
Week 13	Day 92	92	89	102
Week 16	Day 113	113	103	116

Week 17	Day 120	120	117	130
Week 20	Day 141	141	131	144
Week 21	Day 148	148	145	158
Week 24	Day 169	169	159	172
Week 25[a]	Day 176	176	173	190
Week 25[b]	Day 176	176	173	195
Week xx[b]	Day 214	214	196	236
Week xx[b]	Day 259	259	237	273

[a]: For Cohorts D1, D2 participants who enter Part 2 after Part 1 treatment period.

[b]: For Cohorts D1, D2 participants who do not enter Part 2 after Part 1 treatment period.

Windowing of the safety follow up visits in Part 1 (i.e. Day 214 and Day 259 for those participants from Cohorts D1 and D2 who do not enter Part 2 after Part 1 treatment period), Day 1 and unscheduled/ET visits in Part 2 for endpoints assessed every 4 weeks in Part 2 will follow the table below:

Analysis Visit	**Target Day**	**Study days for unscheduled/ET visit**	
		Lower Bound (inclusive)	**Upper Bound (inclusive)**
Week 24	169	156	183
Week 28	197	184	211
Week 32	225	212	239
Week 36	253	240	267
Week 40	281	268	295
Week 44	309	296	323

Week 48	337	324	351
Week 52	365	352	379
Week ww	ww *7 +1	ww*7-12	ww*7+15

For endpoints with assessment every 12 weeks in Part 2, i.e. HHD [redacted], their safety follow up visits in Part 1 (i.e. Day 214 and Day 259 for those participants from Cohorts D1 and D2 who do not enter Part 2 after Part 1 treatment period), Part 2 Day 1, unscheduled/ET visits will be mapped as follows.

Analysis Visit	**Target Day**	**Study days for unscheduled/ET visit**	
		Lower Bound (inclusive)	**Upper Bound (inclusive)**
Week 24	169	156	183
Week 28	197	184	225
Week 40	281	253	309
Week 52	365	337	393
Week 64	449	421	477
Week 76	533	505	561
…	….	…	…
Week ww	ww *7 +1	ww*7-28	ww*7+28

[redacted]

Mapping of visits in Part 2 will depend on the Day 1 of Part 2.

- First, study day since Part 1 baseline for Part 2 Day 2 will be compared with the above table for windowing unscheduled/ET visits.
- If the Day 1 of Part 2 falls in the study day interval for Week 28, then the subject's visits in Part 2 will be mapped continuing the sequence of visits in Part 1 starting from Week 28, Week 32 etc.
- If the Day 1 of Part 2 falls into a window corresponding to a later analysis visit than Week 28, then all the remaining visits in Part 2 will be shifted accordingly. For example, if the Day 1 of Part 2 falls into the interval for Week 32, then the remaining visits in Part 2 will be labeled Week 36, Week 40 etc as follows.

Analysis Visit	**Part 2 visit if Day 1=> Week 28**	**Part 2 visit if Day 1 => Week 32**	**Part 2 visit if Day 1 => Week 36**
Week 28	Day 1	<skipped>	<skipped>
Week 30	Day 15	<skipped>	<skipped>
Week 32	Day 29	Day 1	<skipped>
Week 36	Day 57	Day 29	Day 1
Week 40	Day 85	Day 57	Day 29
Week 44	Day 113	Day 85	Day 57

Week 48	Day 141	Day 113	Day 85
Week 52	Day 169	Day 141	Day 113
…	…	…	…

For endpoints with assessment every 12 weeks in Part 2, i.e. HHD, [redacted] their visits will be mapped as follows.

Analysis Visit	**Part 2 visit if Day 1=> Week 28**	**Part 2 visit if Day 1 => Week 32**
Week 28	Day 1	<skipped>
Week 30		<skipped>
Week 32		Day 1
Week 40	Day 85	Day 85
Week 52	Day 169	Day 169
Week 64	Day 253	Day 253
…	…	…

[redacted]

[redacted]

Mapping visits may be handled case by case as well, if appropriate.

Visit mapping for other endpoints will follow the same logic as ALSFRS-R.

3.2. Study Treatment

In Part 1

Participants with ALS:

Cohort A: BIIB105 5 mg or placebo

Cohort B: BIIB105 20 mg or placebo

Cohort C1: BIIB105 60 mg or placebo

Cohort D1: BIIB105 120 mg or placebo

Participants with polyQ-ALS:

Cohort C2: BIIB105 60 mg or placebo

Cohort D2: BIIB105 120 mg or placebo

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 oce every 4 weeks (on Days 57, 85, 113, 141, and 169), for a total of 8 doses over approximately 25 weeks.

In Part 2:

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, based on Sponsor review of emerging safety, PK, PD, and/or clinical data from the study, to doses up to 120 mg. The 60 mg dose in Part 2 was increased to 120 mg following the SST review on 13 December 2023. Doses in Part 2 may also be decreased, based on Sponsor review of emerging safety, PK, PD, and/or clinical data from the study.

3.3. Subgroup Variable

As no notable difference was observed across all efficacy/safety endpoints in interim analyses, no subgroup analyses are planned for final CSR.

3.4. Analysis Sets

Part 1

1) Part 1 FAS Population

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.

2) Part 1 Safety Analysis Population

The Part 1 safety analysis population is defined as all randomized participants who received at least 1 dose of study treatment in Part 1. In the case of any subjects who are mis-randomized, then any analyses based on the safety analysis population will be based on actual treatment received.

3) Part 1 PK Analysis Population

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.

4) Part 1 PD Population

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.

5) Part 1 Clinical Function Population

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.

Part 2

1) Part 2 FAS Population

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

2) Part 2 Safety Analysis Population

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

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.

3.5. Treatment Group

In the integrated safety and PK summary of Part 1 and Part 2, summaries and analyses will be presented by treatment received for the subjects in the safety population defined previously. The following treatment group will be considered for the safety data:

- BIIB105 Pool 120 mg DL: this group includes Cohorts D1 and D2 participants who received at least one dose of BIIB105 120 mg in Part 1 or Part 2, i.e. total of all subjects in Part 1 Cohorts D1 and D2 exposed to BIIB105 120 mg during Part 1 (i.e. DL1) or initiated during Part 2 (DL2). Data since their first dose of BIIB105 120 mg will be included.
- BIIB105 Pool 60 mg: this group includes the participants who received at least one dose of BIIB105 60 mg in Part 1 or Part 2. The 60 mg dose in Part 2 was increased to 120 mg starting December 2023. Data since their first dose of BIIB105 60 mg and before their first dose of 120 mg will be included in analysis for this pool. Baseline is defined as first dose of BIIB105 60 mg.
- BIIB105 Pool 120 mg: this group includes the participants who received at least one dose of BIIB105 120 mg in Part 1 or Part 2. Data since their first dose of BIIB105 120 mg will be included. Baseline is defined as first dose of BIIB105 120 mg. In addition to participants from BIIB105 Pool 120 mg DL, this group will also include Cohort A, B, C1, and C2 participants who received at least one dose of BIIB105 120 mg in Part 2, i.e. participants escalated from 60 mg to 120 mg in Part 2.

In the integrated efficacy and biomarker summary of Part 1 and Part 2 for D1 and D2, pooled group "DL" includes cohorts D1 and D2 subjects in Part 1 clinical function population or PD population and data since their first dose of study drug treatment in Part 1 will be included. The following treatment group will be considered for the efficacy data:

- Placebo/Delayed-start BIIB105 120 mg: this group includes the Cohorts D1 and D2 subjects in the Part 1 FAS population who were on placebo in Part 1, who may or may not roll over to Part 2 and start active treatment with BIIB105. Data since their first dose of study drug treatment in Part 1 will be included. Baseline is defined as the Day 1 of Part 1.
- Early-start BIIB105 120 mg: this group includes the Cohorts D1 and D2 subjects in the Part 1 FAS population who were on BIIB105 120 mg in Part 1, who may or may not continue their study treatment in Part 2. Data since their first dose of 120 mg in Part 1 will be included. Baseline is defined as the Day 1 of Part 1.

4. List of Planned Study Analyses

4.1. Interim Analysis

An interim analysis of unblinded key safety, secondary, [redacted] endpoints (including PK, PD, clinical function) for Part 2 and integrated analyses of Part 1 and Part 2 was conducted following the completion of Day 175/176 visit for all Part 1 subjects to inform decisions on the BIIB105 clinical development program, the database lock date was April 29, 2024.

4.2. End of Long-term Follow-up Analysis

As the study is early terminated by sponsor, analysis of key safety, secondary, [redacted] endpoints (including PK, PD, clinical function) for Part 2 and integrated analysis of Part 1 and Part 2 will be conducted.

5. Statistical Methods for Planned Analyses

5.1. General Principles

Descriptive summary statistics will be presented for all primary, secondary, and [redacted] endpoints collected. Unless otherwise specified, for continuous endpoints, the summary statistics will generally include number of subjects with data, mean, standard deviation, median, first and third quantiles and range. For categorical endpoints, the summary statistics will generally include number of subjects with data, and frequent counts the percentage of those with data in each category.

As a general rule, any visit/dose group combination that only has data for 1 participant will not be presented in group plots. All data will be listed, unless otherwise specified.

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

5.2. Participant Accountability

Analyses in this section will be analyzed for Part 2 FAS population and integrated Part 1 and Part 2 FAS population. For Part 2, the summaries will be presented by initial dose level in Part 2 (BIIB105 60 mg vs BIIB105 120 mg), and for all subjects combined. Selected summaries for Part 2 Cohorts D1+D2 may also be summarized by treatment assignment in Part 1 (120 mg [Cohorts D1+D2] and Placebo [Cohorts D1+D2]). For integrated Part 1 and Part 2, the summaries will be presented by treatment assignment in Part 1 for subjects in Cohorts D1 and D2.

For Part 2, the number (and percentage) of subjects dosed; completed the treatment; completed the study; completed the study but missed one or more doses; discontinued treatment and the reasons for discontinuation; and withdrew from study early and the reasons for withdrawal will be summarized in a table. The number of subjects who enrolled and completed study will be summarized.

For integrated Part 1 and Part 2, number (and percentage) of subjects dosed in Part 1, dosed in Part 2, ongoing in Part 1 at interim, ongoing in Part 2 at interim, died in Part 1, died in Part

2, discontinued treatment and reasons for discontinuation, and withdrew from study early and the reasons for withdrawal will be summarized in a table.

A listing of subjects who discontinued treatment/withdrew from study and the associated reasons for discontinuation/withdrawal will be presented.

5.3. Medical History

A summary of medical history will be presented for Part 2 by initial dose level in Part 2. Medical history will be classified using MedDRA version 24.1 or later if available. A summary of medical history by system organ class and preferred term will also be provided.

5.4. Protocol Deviations

For Part 2, protocol deviations identified during site monitoring will be captured in a protocol deviation log. All protocol deviations will be listed and a summary of major protocol deviations by initial dose level in Part 2 will also be provided. For subjects who escalate from 60 mg to 120 mg in Part 2, protocol deviations after their first dose of escalation to 120 mg will be summarized separately.

5.5. Study Treatment Exposure and Concomitant Medications and Non-Drug Treatments/Procedures

Extent of exposure to study treatment will be summarized for Part 2 by initial dose level. Number of participants who received BIIB105 60 mg or BIIB105 120 mg in Part 2 will be summarized by initial dose, as well as total cumulative dose in mg.

Study drug compliance percentage up to the last dose of study drug received in Part 2 will be defined as the number of doses actually received divided by the number of doses that the subject is expected to receive during the Part 2 study period and will be summarized descriptively and categorically (<80%, 80%-90%, 90%-100%). For participants who withdrew from Part 2 early, the number of expected doses is the planned number of doses before the time of withdrawal.

Duration of exposure and time on study will be summarized descriptively by initial dose. Duration of exposure will be calculated as (last dose date – first dose date +1) in days and time on study will be calculated as (end of study date – first dose date +1) in days.

Concomitant Medications and non-drug treatment/procedures will be analyzed for Part 2 by initial dose level. For subjects who escalate from 60 mg to 120 mg in Part 2, concomitant medications and non-drug treatments/procedure with start date after their first dose of escalation to 120 mg will be summarized separately.

Concomitant medications will be coded using the World Health Organization (WHO) dictionary WHODRUG (Mar 2024) and concomitant non-drug treatments/procedures using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later if available.

Medications and non-drug treatments are considered concomitant if they are taken during the study. This includes medications/treatment/procedures that were started prior to the date and

time of first dose of study drug if their use continued on or after the date and time of first dosing. If the start date is available but start time is missing and the medication/non-drug treatment start date is the same as the first dose date, the medication/non-drug treatment will be considered concomitant. Similarly, if the stop date is available but stop time is missing and the medication/non-drug treatment stop date is the same as the first dose date, the medication/non-drug treatment will also be considered concomitant. Medications/therapies with missing start or stop dates and times, will also be considered as concomitant in the following situations:

- If both the start and stop dates and times of a medication/treatment/procedure are missing.
- If the start date and time of a medication/treatment/procedure is missing and the stop date and time of the medication/therapy occurred on or after the date and time of first dose of study drug.
- If the start date and time of a medication/treatment/procedure therapy occurred prior to the date and time of first dose of study drug and the stop date and time of the medication/treatment/procedure is missing and the medication/treatment/procedure is listed as ongoing.

If the start date and time of a medication/treatment/procedure occurred prior to the date and time of first dose of study drug and the stop date and time of the medication/treatment/procedure is missing and the medication/therapy is not listed as ongoing, then the medication/treatment/procedure will be considered as concomitant.

The number and percentage of subjects taking any concomitant medications will be summarized for the safety population. The number and percentage of subjects taking any concomitant non-drug treatments and disallowed concomitant medications will also be summarized for the safety population.

5.6. Efficacy Endpoints

5.6.1. General Analysis Methods for Efficacy Endpoints

Covariates

The covariates for the statistical models in the integrated analysis for participants from Cohorts D1 and D2 will be based on Part 1 baseline and will be as follows:

- Corresponding baseline score for the endpoint (continuous)
- Baseline disease duration from onset of symptoms to the first dose of study treatment as derived in Appendix 1, i.e. time since symptom onset in months (continuous)
- Baseline plasma NfL
- Riluzole or Edaravone use which will take 3 levels as follows:
    - Edaravone Use (Edaravone = Yes; Riluzole = Yes OR No)
    - Riluzole Only (Riluzole = Yes and Edaravone = No)

- Neither (Edaravone = No and Riluzole = No)

Edaravone use may only occur for a very small number of subjects in which case this could cause problems for statistical modelling. If Edaravone use is limited to <5 subjects within the relevant population then riluzole and edaravone use will be combined so that there are only 2 levels:

- Edaravone or Riluzole Use (Edaravone = Yes and Riluzole = Yes; OR Edaravone = Yes and Riluzole = No; OR Edaravone = No and Riluzole=Yes)
- Neither (Edaravone = No and Riluzole = No)

Missing data for individual items in scales

The imputation of individual components of each endpoint are described in Section 5.6.2. Imputation will be performed within a scale for each endpoint by prorating the observed scores at the same visit, for example, if there are missing responses to some of the individual questions on a scale at a given visit the endpoint may only be derived for that visit if there are a certain number of individual items/components with available data. Specific details are provided for each assessment/scale, as this differs across assessments/scales. These imputations within a visit will be performed prior to applying imputations on the endpoint at the visit level (e.g. multiple imputation) and will be applied consistently across visits where required. Multiple imputation will not be applied on an individual item/question within an assessment/scale.

Multiple imputation (MI)

Missing data for postbaseline assessments will be imputed using the multiple imputation method [Schafer 1997, Schafer 1999]. Visit windowing as described in Section 4.5 will be applied prior to any imputations. Any imputation on an item level within a scale will be performed prior to performing MI.

MI will be performed on actual values, domains, total scores or summary scores depending on the endpoint and not performed at the item level; the complete datasets can then be used to calculate change from baseline.

All available data will be used where subjects have missed doses but continued to perform assessments; otherwise any missing values will be imputed using MI. The Markov Chain Monte Carlo (MCMC) will be used to impute the missing postbaseline scores in the endpoint by treatment group.

Prior to performing multiple imputation, the dataset will be sorted by ascending unique subject identifier (USUBJID). The treatment variable will be coded so that or early-start BIIB105 120 mg is set to 0 and placebo/delayed-start BIIB105 120 mg is set to 1 for inclusion in the MI model. Similarly, two level riluzole/edaravone use will be set to 0 for

no use (i.e. neither riluzole or edaravone) and 1 for use of either riluzole or edaravone or both. When three level riluzole/edaravone use is used, two binary variables (edaril3cat1 and edaril3cat2) will be coded, where both variables will be set to 0 for no use (i.e. neither riluzole or edaravone), edaril3cat1 is set to 1 and edaril3cat2 is set to 0 for use of riluzole only, and edaril3cat is set to 0 and edaril3cat2 is set to 1 for edaravone use. The variable list in the model for imputations will include treatment group, riluzole/edaravone use, the corresponding baseline value for the endpoint, and all available postbaseline values. The MI model will be performed by treatment group. A set of 100 complete imputed datasets will be generated. This number of imputed datasets needs to be large enough for applying the multiple imputation method in this study as the sample size is small. The relative efficiency parameter will also be checked to determine the acceptability of the imputed results i.e. it should be close to 98% or higher. The seed used for the multiple imputation is specified in Table 2.

Table 2: Seed used for each endpoint in MI

Endpoint	Seed
ALSFRS-R Bulbar function Respiratory function Fine motor skills Gross motor skills (Total score will not be imputed separately; instead the imputed datasets from the functional domains will be used to calculate the total score. A separate model will be used for each functional domain.)	8492382
Percent predicted SVC	6734934
HHD megascore (overall, upper extremities, lower extremities)	3748311
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Imputed values that are outside of the expected range of a scale will be reset: for example, for ALSFRS-R bulbar function should only be in the range 0 to 12. Values outside of this

range will be reset so that values below 0 are set to 0 and values above 12 are set to 12. Values will be used as imputed,and will not be rounded prior to analysis.

For each of the 100 imputed datasets, change from baseline will be calculated using the imputed datasets, and the change from baseline endpoint will be compared between treatment groups using an ANCOVA model for continuous endpoints (efficacy and pharmacodynamic endpoints). The ANCOVA model will include covariates for each of the corresponding baseline value for the endpoint, baseline plasma NfL, baseline disease duration since symptom onset, and use of riluzole or edaravone. The model will be used to present overall LS means and standard errors for each treatment group, and LS mean differences for treatment with corresponding 95% CI and p-values. A combined estimate of the LS means, LS mean differences and standard errors of the 100 imputed datasets will be obtained, where standard errors will be used to obtain 95% CI from PROC MIANALYZE [Little et al, 2002]. Separate ANCOVA models will be used to obtain estimates, 95% confidence intervals and p-values for other visits. For subjects who died, the imputed values after death will be used in the ANCOVA analysis eg change from baseline in ALSFRS-R.

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, ANCOVA model will be performed for Early-start BIIB105 120 mg vs. Placebo/Delayed-start BIIB105 120 mg.

Presentation of Data

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, broad ALS/polyQ ALS, 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. LS mean changes over time will be also presented in line plots.

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

Due to the washout period between Part 1 and Part 2 for all participants in Cohorts A, B, C1, and C2, Part 2 clinical function data for these cohorts will be presented separately from Part 1. Descriptive summaries will be presented for the combined cohort (A+B+C1+C2) by their initial dose level, i.e. 60 mg in Part 2 with baseline defined as Part 2 baseline. As participants on the 60 mg dose in Part 2 were increased to 120 mg starting December 2023, visits since first dose escalation to 120 mg will not be included in the analysis for Part 2 BIIB105 60 mg.

Table 3: Analysis Methods for Part 2 and Integrated Summary of Efficacy and PD Data

Endpoint	Summary/ Analysis	Part 2	Integrated Part 1 and Part 2
		BIIB105 60 mg	Pool DL (Placebo/delayed-start BIIB105 120 mg And Early-start BIIB105 120 mg)
Absolute value/change in ALSFRS-R total score since Part 1 baseline	Observed data all visits descriptive		x
Absolute value/change in ALSFRS-R total score since Part 2 baseline	Observed data all visits descriptive	x	
Change in ALSFRS-R total score by selected time points since Part 1 baseline	MI data + ANCOVA		x
Absolute value/change in percent predicted SVC since Part 1 baseline	Observed data all visits descriptive		x
Absolute value/change in percent predicted SVC since Part 2 baseline	Observed data all visits descriptive	x	
Change in percent predicted SVC by selected time points since Part 1 baseline	MI data + ANCOVA		x
Absolute value/change in HHD megasocre since Part 1 baseline	Observed data all visits descriptive		x
Absolute value/change in HHD megascore since Part 2 baseline	Observed data all visits descriptive	x	
Change in HHD megascore by selected	MI data + ANCOVA		x

time points since Part 1 baseline			
Time to event endpoints since Part 1 baseline	K-M plot Cox model		x
[redacted]			
[redacted]			

5.6.2. ALSFRS-R

General Description

The ALSFRS-R is a questionnaire to measure degree of impairment in 4 functional domains: respiratory function, bulbar function, gross motor skills, and fine motor skills. Each domain consists of 3 items, each scored from 0 to 4, with higher scores representing better function. The Each domain can have maximum score of 12 and the total possible score for ALSFRS-R is 48. The items for each domain are listed below.

- Respiratory function: dyspnea, orthopnea and respiratory insufficiency
- Bulbar function: speech, salivation and swallowing
- Gross motor skills: turning in bed, walking and climbing Stairs

- Fine motor skills: handwriting, cut and handling utensils without or with gastrostomy, dressing and hygiene

General Considerations

Descriptive statistics for ALSFRS-R total score at each visit and their change from baseline will be summarized by treatment group. Corresponding plots will also be generated.

Descriptive analyses will be performed in the FAS population.

The total score is the sum of the 4 functional domain scores or all individual item scores if no missing item scores are present. Each domain score is the sum of scores of 3 items for that domain. For missing item scores, the total score and domain scores will be derived as described in the missing data section below.

Missing Data

A summary of missing data for ALSFRS-R total score will be presented based on observed data by treatment group and visit.

Missing data at each visit will not be imputed.

If there are missing data at item level, ALSFRS-R total and domain scores will be derived as below.

- The ALSFRS-R total score will be considered missing if more than 3 individual item scores are missing.
- If no more than 3 (≤ 3) individual item scores are missing and a functional domain has at least one individual item score available, the functional domain score with any missing item score(s) will be calculated by the following formula:

  ALSFRS-R domain score = [(average of all answered item scores) x 3].

  The total score will be the sum of the 4 functional domain scores.

- If 3 individual item scores are missing from the same functional domain, then the ALSFRS-R domain score is considered as missing and the total score is calculated by the following formula:

ALSFRS-R total score = average of all answered item scores from other 3 domains x

Descriptive statistics

Descriptive statistics, including ALSFRS-R total and change from baseline in the ALSFRS-R total scores, will be evaluated by visit with descriptive statistics (mean, SD, median, 1st and 3rd quartiles, range) for pooled group DL and Part 2 BIIB105 60 mg in the FAS population.

Spaghetti plots will be presented by treatment group.

Statistical Analyses

The following analyses will be performed for pooled group DL in the FAS population.

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, difference between treatment groups (i.e. Early-start BIIB105 120 mg and Placebo/Delayed-start BIIB105 120 mg) in least square means of Week 40 change from baseline with corresponding standard errors and 95% confidence intervals taken from the ANCOVA described in Section 5.6.1 based on the multiple imputation dataset.

5.6.3. HHD Megascore

General Description

Twenty-two muscles in 11 pairs are examined in both upper and lower extremities (left and right shoulder flexion, left and right elbow flexion, left and right elbow extension, left and right wrist extension, left and right abduction index finger, left and right abduction thumb, left and right abduction 5th digit, left and right hip flexion, left and right knee flexion, left and right knee extension, left and right ankle dorsiflexion).

Each muscle is tested at least twice. If the difference between the first two trials is greater than 15%, or if the evaluator thinks that one of the first two trials was not valid, a third trial may be performed. The maximum value of the two highest measures within 15% variability will be used for the analysis. If there is no pair with ≤15% variability, then the maximum value of the two values that are closest together will be used for the analysis.

Missing Data

Missing data at each visit will not be imputed.

For any missing muscle strength with a reason of "UNABLE TO TEST", the missing strength will be imputed as 0.

The megascore will be considered missing if more than 14 measures on individual muscles are missing. If no more than 14 (≤ 14) measures are missing out of 22 total measures, the megascore calculation steps for each subject at each visit steps are listed below:

- Calculate baseline mean and SD for each individual muscle from all subjects;
- Normalize results to Z-score for each subject at each visit for each individual muscle as:

$$Z - score = \frac{Observed\ result\ (muscle\ strength) - baseline\ mean}{baseline\ SD}$$

- Average Z-scores across all individual muscles to obtain the overall megascore for each subject at each visit.

Missing data of HHD megascore for postbaseline assessments will be imputed using the multiple imputation method as descripted in Section 5.6.1.

Descriptive Statistics

Descriptive statistics, including observed value and change from baseline in the HHD megascore, will be evaluated by visit with descriptive statistics (mean, SD, median, 1st and 3rd quartiles, range) for pooled group DL and Part 2 BIIB105 60 mg in the FAS population.

Spaghetti plots will be presented by treatment group.

Statistical Analyses

The following analyses will be performed for pooled group DL in the FAS population.

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, difference between treatment groups (i.e. Early-start BIIB105 120 mg and Placebo/Delayed-start BIIB105 120 mg) in least square means of Week 40 change from baseline with corresponding standard errors and 95% confidence intervals taken from the ANCOVA described in Section 5.6.1 based on the multiple imputation dataset.

5.6.4. Percent Predicted SVC

General Description

Vital capacity will be measured by means of the slow vital capacity (SVC) test using a facemask with the participant sitting upright. SVC will be determined by performing at least 3 trials. If the difference between the two highest values of the three trials is ≥10%, then up to 5 trials may be performed. The highest percent predicted SVC value at each visit will be used for the analysis.

Descriptive Statistics

Descriptive statistics, including observed value and change from baseline in the percent predicted SVC, will be evaluated by visit with descriptive statistics (mean, SD, median, 1st and 3rd quartiles, range) for pooled group DL and Part 2 BIIB105 60 mg in the FAS population.

Spaghetti plots will be presented by treatment group.

Statistical Analysis

The following analyses will be performed for pooled group DL in the FAS population.

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, difference between treatment groups (i.e. Early-start BIIB105 120 mg and Placebo/Delayed-start BIIB105 120 mg) in least square means of Week 40 change from baseline with corresponding standard errors and 95% confidence intervals taken from the ANCOVA described in Section 5.6.1 based on the multiple imputation dataset.

5.6.5. Time to Event Analyses

Time-to-event endpoints include

- 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, permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days), or withdrawal from study due to disease progression.

Time to event endpoints will be summarized using Kaplan-Meier curves based on randomization in Study 275AS101 Part 1.

Participants without an event will be censored at the last known alive dates, defined as the interim cut date for 275AS101 (March 12, 2024) or as the last date in the database with any actual study visit or measurements indicating their alive status.

Summary of time-to-event data will be presented by treatment group including number of participants with the event (separate by each individual event for composite event) and number of participants who were censored. Kaplan-Meier plots will be presented. The median survival time, percentiles (5^{th}, 10^{th}, 25^{th}, 75^{th}) and associated 95% confidence limits, and proportion of participants with an event at a list of time points (Week 26, 52, 78, etc.) will be estimated using the Kaplan-Meier. Treatment comparison for time to event will be based on a log rank test. A Cox proportional hazards model will be used to obtain the hazard ratio and 95% confidence intervals. The Cox proportional hazards model may include covariates such as baseline disease duration since symptom onset, baseline plasma NfL, and riluzole or edravone use (as specified in Section 5.6.1 under Covariates). P-value from the log rank test of the survival function will be provided. Hazard ratio (and corresponding 95% CI) comparing the treatment group will be obtained from Cox proportional hazard model. The log-rank test may be stratified by median baseline plasma NfL.

Whether a participant has had a permanent ventilation event, defined as (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days), will be calculated using participant- and site-reported ventilation data from a weekly participant e-diary and from the eCRF, respectively. These data provide a yes/no answer as to whether a participant has used mechanical ventilation for ≥22 hours on each date (s)he has participated in the study. A participant will have reached the event of permanent ventilation if there is a "yes" answer on 21 or more consecutive days. The event will be defined as the first day of the ≥21 consecutive days with a "yes" answer. If there are dates in which there are discrepancies between the participant's e-diary answer and the site's eCRF answer, the eCRF data will supercede the e-diary data.

Due to the delay in the eCOA vendor, there are participants in Cohorts D1/D2 who did not have the ventilation e-diary at Day 1. To impute the ventilation event from these participants' Day 1 and their first date e-diary, two approaches will be used. The primary analysis will utilize the participants' closest ALSFRS-R Q12 answer available for respiratory insufficiency after their ediary initiation. If the participant responded 2 (continuous use of Bipap during the night), 3 (intermittent use of Bipap), or 4 (None), the mechanical ventilation use ≥22 hours for the dates between the date the participant's ALSFRS-R questionnaire date and its prior

questionnaire date will be imputed as "no". If the participant responded 1 (continuous use of Bipap during the night and day), the mechanical ventilation use ≥22 hours for the dates between the date of the participant's ALSFRS-R questionnaire date and its prior questionnaire date will be imputed as "yes". If the participant responded 0 (invasive mechanical ventilation by intubation or tracheostomy), the mechanical ventilation use ≥22 hours for the dates between the date of the participant's ALSFRS-R questionnaire date and its prior questionnaire date will be imputed as "unknown". Another approach is to impute the ventilation event for these gap dates as "yes" on trailing ventilation events since participants' first ediary date, i.e., imputing "yes" for all missing e-diary dates if the first available e-diary entry after the missing dates is "yes". If the second approach gives different imputation for any of the gap dates, a sensitivity analysis will be performed.

For dates with answers of "unknown" and missing gaps in the final data, available ALSFRS-R Q12 for respiratory insufficiency within 30 days window will be utilized in the same way as mentioned above to impute the ventilation status. Ventilation status will be imputed as "no" unless evidence of ventilation support from any source of data.For analysis of integrated data from Part 1 and Part 2, analyses will be conducted to compare Early-start BIIB105 120 mg versus Placebo/Delayed-start BIIB105 120 mg groups.

The subgroup analyses will be conducted by median baseline plasma NfL level.

Time to event since ALS symptom onset analyses might be performed post hoc if needed.

5.6.6. Subgroup Analyses for Efficacy Endpoints

- As no notable differences were observed in the interim analyses, no subgroup analyses are planned.

5.7. Safety Endpoints

The safety population will be used for the analyses of the safety data. Safety data will be summarized using descriptive statistics by dose level and/or cohort.

Adverse events (AEs) and serious adverse events (SAEs), and CSF laboratory data, will be evaluated for safety. Safety data will be summarized using descriptive statistics.

For analyses of Part 2, safety data will be summarized by their initial dose level in Part 2 (BIIB105 60 mg vs BIIB105 120 mg), with baseline defined as the first dose of BIIB105 60 mg or BIIB105 120 mg in Part 2. [redacted] For participants who escalate from 60 mg to 120 mg in Part 2, AEs and CSF laboratory data since their first dose escalation to 120 mg will be summarized separately.

For integrated analyses of Part 1 and Part 2 for Cohorts D1 and D2, selected 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. As participants on the 60 mg dose in Part 2 was increased to 120 mg starting December 2023, data since their first dose of escalation to 120 mg will not be included in the analysis for 60 mg BIIB105. To assess the overall safety profile of 120 mg 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, which also includes participants escalate from 60 mg to 120 mg in Part 2.

Table 4. Pooled Groups for Safety Endpoints.

Pooled Group	**Pool BIIB105 120 mg DL**	**Pool BIIB105 60 mg**	**Pool BIIB105 120 mg**
Treated Periods	BIIB105 120 mg treated period	BIIB105 60 mg treated period	BIIB105 120 mg treated period
Participants Included	Total of all participants in Part 1 Cohorts D1 and D2 exposed to BIIB105 120 mg during either Part 1 (i.e. DL1) or initiated during Part 2 (DL2); regardless of whether they entered Part 2. Note a subset of tables will be presented for DL1 and DL2.	All participants who received at least one dose of BIIB105 60 mg in either Part 1 or Part 2.	All participants who received at least one dose of BIIB105 120 mg in either Part 1 or Part 2.
Data Included	All data from BIIB105 120 mg during Part 1 and Part 2. For those who initiated BIIB105 120 mg in Part 2, data from Part 1 are not included here	All data since first dose of BIIB105 60 mg, and before their first dose of escalation to 120 mg in Part 2.	All data since first dose of BIIB105 120 mg.

Table 5: Analysis Methods for Part 2 and Integrated Summary of Safety Data

Endpoints	Summary/Analysis	Part 2		Integrated Part 1 and Part 2		
		60 mg	120 mg	Pool BIIB105 120 mg DL (DL1, DL2)	Pool BIIB105 60 mg	Pool BIIB105 120 mg
Disposition	Accounting of participants	x	x	x		
Medical history	Summary	x	x			
Concomitant medications	Summary	x	x			
Adverse event	Overall summary AE by SOC and PT SAE by SOC and PT Adjusted incidence rate	x	x	x	x	x
CSF lab tests	Shift table Spaghetti plots Post-baseline evaluation of CSF WBC and CSF protein	x	x	x	x	x
Other lab tests	Descriptive analysis, shift table	x	x			
Vital Signs	Descriptive analysis	x	x			
ECG	Descriptive analysis, shift table	x	x			
Neurological Examination	Descriptive analysis	x	x			
PK	CSF concentration descriptive statistics	x		x		

5.7.1. Adverse Events

All AEs will be classified using MedDRA version 24.1 or later if available. Only treatment emergent AEs (TEAEs) will be summarized, where treatment emergence will be relative to the first dose of study drug. A treatment emergent AE/SAE is defined as any AE/SAE with an onset date that is on or after the first dose of study drug or any pre-existing condition that has worsened in severity after the first dose of study drug. Whenever possible,

date/time will be used to determine whether an event is treatment emergent. If an event date (start or end) is incomplete, a TEAE will be determined assuming most conservate way as follows:

- If onset day is missing and the month and year are the same as or after the treatment start date, then that event is considered treatment emergent.
- If both onset month and day are missing and the year is the same as or after the treatment start date, then that event is considered treatment emergent.
- If both onset date and end date are completely missing, an event will be considered as a TEAE.
- If onset date is completely missing and end date is not missing which is after the first dose of study drug, an event will be considered as a TEAE.

The incidence of TEAEs will be summarized by dose level (or cohort) and overall BIIB105 as follows:

- Overall summary of TEAE
- TEAEs by primary SOC and MedDRA preferred term
- TEAEs by MedDRA preferred term
- SAEs by primary SOC and MedDRA preferred term
- Related SAEs by primary SOC and MedDRA preferred term
- TEAEs by CTCAE grading, primary SOC and MedDRA preferred term
- TEAEs with severity greater than or equal to 3 by primary SOC and MedDRA preferred term
- Related TEAEs by primary SOC and MedDRA preferred term
- TEAEs that led to discontinuation of study treatment by primary SOC and MedDRA preferred term
- TEAEs that led to withdrawal from study by primary SOC and MedDRA preferred term
- TEAEs related to the lumbar puncture by primary SOC and MedDRA preferred term.
- TEAEs that led to death by primary SOC and MedDRA preferred term

For the summary of TEAEs by severity, primary system organ class and/or preferred term, participants will be counted only once within each primary SOC/MedDRA preferred term and will only be counted under the maximum severity.

For the summary of TEAEs by relationship to study treatment, a participant will be counted only once and in the category of the strongest relationship to study treatment within each SOC/preferred term. The relationship to study treatment will be classified as related or not related.

Listings of all AEs, SAEs, AEs that led to study drug discontinuations, and AEs that led to study withdrawals will be presented. Listing of death will be provided.

5.7.2. Laboratory Data

Laboratory data will be evaluated to determine the incidence of abnormalities that emerge during the study. Changes in laboratory evaluations will be presented relative to baseline, which is defined as the closet visit prior to the participant's start treatment. Baseline value is defined as data collected which are prior to and/or on the date of the first dose, usually also the same day as the Day 1 visit. If there is more than one value on or before Day 1, then the last non-missing value prior to (including on) the date of first dose will be used as the baseline value.

The following clinical laboratory parameters will be assessed in the protocol:

- Hematology panel: complete blood count with differential
- Blood chemistry panel: 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)
- CSF analysis: red blood cell count, white blood cell count, protein, and glucose.
- Coagulation: PT (prothrombin time), aPTT (activated partial thromboplastin time), and INR (international normalized ratio).

Shift analyses

Each hematology, blood chemistry, coagulation, and CSF laboratory parameter will be flagged as "low" or "high" relative to the parameter's normal range or as "unknown" if no results is available. All visits with available results, including unscheduled visits, will be included in shift analysis.

For each urinalysis laboratory parameter, the number and percentage of participants experiencing post-dosing shifts to abnormal will be summarized.

For each hematology, blood chemistry, coagulation, and CSF laboratory, the number and percentage of participants experiencing post-dosing shifts to "low" or "high" will be summarized. Shift to low includes results from normal to low, high to low, and unknown to low. Shift to high includes results from normal to high, low to high, and unknown to high. In each summary, the denominator for the percentage is the number of participants at risk for the shift. The number at risk for the shift to low is the number of participants whose baseline values is not low and who have at least one post-baseline value. The number at risk for the shift to high is the number of participants whose baseline value is not high and who have at least one post-baseline value. A participant will be counted only once for each parameter and each type of shift if there are more than one occurrence for that parameter and that type of shift among post-dosing assessments. Participants with shift will be listed by laboratory parameter and shift type.

Summary of change from baseline and other analysis

In addition to the shift analysis, descriptive statistics (N, mean, SD, median, 1st and 3rd quartiles, and minimum and maximum values) for observed laboratory values, change from baseline and percentage change from baseline in laboratory values of hematology, blood chemistry, and coagulation will be summarized by treatment group and visit. Only scheduled visits will be included in these summaries. Spaghetti plots by site will be presented for CSF samples. Proportion of participants with CSF WBC values above 5, 10, and 20 10^6/L [redacted]

Listing of all chemistry, hematology, coagulation, CSF, and urinalysis values will be provided. Abnormal values will be flagged.

5.7.3. Vital Signs

Summary statistical for actual values will be presented for each visit and vital sign parameters (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure). Weight will be summarized along with vital signs.

The incidence of clinically significant post baseline abnormalities will be summarized per the criteria below:

- Temperature <36°C or >38°C
- Weight 7% or more increase from baseline; 7% or more decrease from baseline
- Systolic blood pressure <90 mmHg or >140 mmHg or >160 mmHg
- Diastolic blood pressure <50 mmHg or >90 mmHg or >100 mmHg
- Pulse rate <60 beats/minute or >100 beats/minute
- Respiratory rate <12 breaths/min or >20 breaths/min

A listing of vital sign data will be provided.

5.7.4. ECG

Triplicate 12-lead electrocardiograms (ECG) are to be collected at the timepoints specified in Schedule of Activities. The continuous (non-categorical) ECG test measured in triplicate includes heart rate, PR interval, QRS interval, QT interval, QTc interval using Fridericia's formula (QTcF) and RR interval. Each triplicate ECG is also interpreted as "normal", "abnormal" or "not evaluated". The number and percentage of participants with shifts from normal to abnormal will be summarized by treatment group. All postbaseline data will be used to identified abnormalities, regardless of whether a scheduled or unscheduled visit.

The mean of the triplicate continuous ECG parameter values at each nominal timepoint will be used for the analyses. If any triplicate within a nominal timepoint is abnormal, the interpretation will be counted as abnormal once for that nominal timepoint.

Baseline for these analyses will be the mean of the replicate values from predose Day 1. If there are no replicates for predose Day 1, then the mean of the replicates from Screening will be used.

The number and proportion of participants whose QTcF results or change values meet certain predefined criteria (listed below) will be summarized.

- Absolute QTcF interval > 450 msec
- Absolute QTcF interval > 480 msec
- Absolute QTcF interval > 500 msec
- Changes from baseline QTcF >30 msec
- Changes from baseline QTcF > 60 msec

A listing of both qualitative and quantitative ECG data will be presented.

5.7.5. Neurological Examination

The neurological examinations include cranial nerves, motor, reflexes, cerebellar function, and mental status (MMSE in Part 1).

For cranial nerves/cerebellar function, a frequency table will be created for the tests of nystagmus, gait, and tremor. The number of participants with the outcomes (Absent, Present, or Not Done for the test of nystagmus, gait, and tremor, and Abnormal, Normal, or Not Done for other tests) will be summarized by treatment group and visit.

For reflexes examination, a frequency table will also be created for the tests of Hoffman signs and plantar response. The number of participants with the outcomes (Absent, Present, Not Done for Hoffman signs and Flexor/Extensor/Undetermined for plantar response) will be summarized by treatment group and visit.

For motor examination, a figure on mean scores vs. visit will be generated by treatment group.

Summary statistics for actual values and change from baseline of the total score of MMSE will be presented for each visit by treatment group. When there are multiple assessments during a single visit, the minimal value will be taken as the value for that visit. A listing of MMSE data will also be provided.

Neurological examinations will be presented in listings as well.

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

The details of derivation and imputation for C-SSRS is described in Appendix 2. The following analyses on C-SSRS measurements will be conducted.

- Descriptive summary of participants who answered “Yes” to any question 1-12 as well as participants who had suicidal ideation or suicidal behavior at baseline and at any post-baseline visit. The denominator for baseline summary is the number of participants who were dosed and had baseline assessment; the denominator for post-

baseline summary is the number of participants who were dosed and had at least one post-baseline assessment for each question.

- Descriptive summary of participants who had treatment-emergent suicidal ideation, participants who had new suicidal ideation as well as participants who had worsening suicidal ideation. The denominator is the number of dosed participants with both baseline and at least one post-baseline suicidal ideation assessment.
- Descriptive summary of participants who had treatment-emergent suicidal behavior. The denominator is the number of participants who answered "No" to all suicidal behavior questions at baseline and had at least one post-baseline suicidal behavior assessment.

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

5.8. Pharmacokinetic Endpoints

The PK population will be used for the analyses of the PK data.

For the PK analysis, the CSF BIIB105 concentrations will be listed and summary statistics (n, mean, SD, median, range, geometric mean and coefficient variation of geometric mean) will be presented by time for each visit. Plots of arithmetic and geometric mean concentration of CSF BIIB105 versus time will be provided if appropriate. Values below limit of quantitation (BLQ) prior to first dosing will be set to 0 and other BLQ will be set to half of lower limit of quantitation (LLOQ). The LLOQ is 0.25 ng/mL for CSF PK.

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]

5.9. Pharmacodynamic and biomarker Endpoints

No pre-specified analyses of pharmacodynamic and biomarker endpoints will be performed for this analysis because there will be no new pharmacodynamic and biomarker data beyond

what was available for the interim analysis will be available. Future analyses may be performed post-hoc.

[redacted]

[redacted]

6. Changes from Protocol-Specified Analyses

- Time to death, incorporating post-study withdrawal or study completion vital status data will not be performed as post-study withdrawal vital status data will not be collected at the time of this analysis.
- Add time to event endpoint of time to death, permanent ventilation (≥ 22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥ 21 consecutive days), or withdrawal from study due to disease progression.

7. References

Protocol 275AS101 Protocol Version 5.0
275AS101 Unblinding Plan Version x.0

[redacted]

[redacted]

Signature Page

Document Name:
BIIB105_275AS101_FINAL_Part2_Integrated_CSR_Final_Statistical_Analysis_Plan_v1.0

Document 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

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