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

Summary

EudraCT number	2016-003225-41
Trial protocol	BE GB DE DK PL ES IT
Global end of trial date	12 August 2024

Results information

Result version number	v1 (current)
This version publication date	28 August 2025
First version publication date	28 August 2025

Trial information

Trial identification

Sponsor protocol code	233AS102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03070119
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the long-term safety and tolerability of BIIB067 (tofersen) in participants with amyotrophic lateral sclerosis (ALS) and confirmed superoxide dismutase 1 (SOD1) mutation. The secondary objectives were to evaluate the pharmacokinetic (PK), pharmacodynamic (PD), biomarker effects, and efficacy of BIIB067 administered to participants with ALS and a confirmed SOD1 mutation.

Protection of trial subjects:

Written informed consent was obtained from each subject’s parent or legal guardian prior to evaluations being performed for eligibility. Adequate time to review the information in the informed consent and ask questions concerning all portions of the conduct of the study was provided. Through the informed consent process, awareness of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken was made. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 67
Worldwide total number of subjects	139
EEA total number of subjects	32

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	122
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled and took part at the investigative sites in Belgium, Canada, France, Germany, Italy, Japan, Denmark, the United Kingdom, and the United States from 08 Mar 2017 to 12 Aug 2024.

Pre-assignment

Screening details:

A total of 139 participants were randomized in the study, of which 95 participants rolled over from Part C and 44 participants rolled over from Parts A and B of the parent study 233AS101 (NCT02623699).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label

Arms

Are arms mutually exclusive?	Yes
Arm title	233AS101: Part C (Prior Placebo)

Arm description:

Participants who were randomized to placebo in Part C of the parent study 233AS101 received 3 loading doses of BIIB067, 100mg, Q2W, on Days 1, 15, and 29 by IT bolus injection in this study followed by up to 90 maintenance doses of BIIB067, Q4W, until the last enrolled participant had their Week 152 maintenance dose visit.

Arm type	Experimental
Investigational medicinal product name	BIIB067
Investigational medicinal product code	ISIS666853
Other name	Tofersen, QALSODY
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects were administered BIIB067, 100 mg, as specified in treatment arm.

Arm title	233AS101: Part C (Prior BIIB067 100 mg)

Arm description:

Participants who were randomized to BIIB067 100 mg in Part C of the parent study 233AS101 received 2 loading doses of BIIB067, 100 mg, on Days 1 and 29, and one dose of BIIB067-matched placebo on Day 15 by IT bolus injection in this study followed by up to 90 maintenance doses of BIIB067,Q4W, until the last enrolled participant had their Week 152 maintenance dose visit.

Arm type	Experimental
Investigational medicinal product name	BIIB067-matching Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects were administered BIIB067-matching placebo as specified in treatment arm.

Investigational medicinal product name	BIIB067
Investigational medicinal product code	ISIS666853
Other name	Tofersen, QALSODY
Pharmaceutical forms	Solution for injection

Routes of administration	Intrathecal use

Dosage and administration details:

Subjects were administered BIIB067, 100 mg, as specified in treatment arm.

Arm title	233AS101: Part A and B (All doses)

Arm description:

Participants who were randomized to BIIB067 or placebo in Part A (at doses 10 mg, 20 mg, 40 mg and 60 mg) or Part B (at doses 20 mg, 40 mg, 60 mg and 100 mg) of the parent study 233AS101 received 3 loading doses of BIIB067, 20 mg, 40 mg, 60 mg, or 100 mg, eventually escalated to 100 mg, 2 weeks apart, and up to 90 maintenance doses, Q4W, by IT bolus injection until the last enrolled participant had their Week 152 maintenance dose visit in this study.

Arm type	Experimental
Investigational medicinal product name	BIIB067
Investigational medicinal product code	ISIS666853
Other name	Tofersen, QALSODY
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects were administered BIIB067, 100 mg, as specified in treatment arm.

Number of subjects in period 1	233AS101: Part C (Prior Placebo)	233AS101: Part C (Prior BIIB067 100 mg)	233AS101: Part A and B (All doses)
Started	32	63	44
Completed	12	34	26
Not completed	20	29	18
Adverse event, serious fatal	7	14	5
Adverse event, non-fatal	-	-	1
Investigator Decision	-	-	1
Lost to follow-up	-	1	-
Disease Progression	5	7	7
Reason not Specified	2	2	1
Consent Withdrawn	6	5	3

Baseline characteristics

Reporting groups	
Reporting group title	233AS101: Part C (Prior Placebo)
Reporting group description:	
Participants who were randomized to placebo in Part C of the parent study 233AS101 received 3 loading doses of BIIB067, 100mg, Q2W, on Days 1, 15, and 29 by IT bolus injection in this study followed by up to 90 maintenance doses of BIIB067, Q4W, until the last enrolled participant had their Week 152 maintenance dose visit.	
Reporting group title	233AS101: Part C (Prior BIIB067 100 mg)
Reporting group description:	
Participants who were randomized to BIIB067 100 mg in Part C of the parent study 233AS101 received 2 loading doses of BIIB067, 100 mg, on Days 1 and 29, and one dose of BIIB067-matched placebo on Day 15 by IT bolus injection in this study followed by up to 90 maintenance doses of BIIB067,Q4W, until the last enrolled participant had their Week 152 maintenance dose visit.	
Reporting group title	233AS101: Part A and B (All doses)
Reporting group description:	
Participants who were randomized to BIIB067 or placebo in Part A (at doses 10 mg, 20 mg, 40 mg and 60 mg) or Part B (at doses 20 mg, 40 mg, 60 mg and 100 mg) of the parent study 233AS101 received 3 loading doses of BIIB067, 20 mg, 40 mg, 60 mg, or 100 mg, eventually escalated to 100 mg, 2 weeks apart, and up to 90 maintenance doses, Q4W, by IT bolus injection until the last enrolled participant had their Week 152 maintenance dose visit in this study.	

Reporting group values	233AS101: Part C (Prior Placebo)	233AS101: Part C (Prior BIIB067 100 mg)	233AS101: Part A and B (All doses)
Number of subjects	32	63	44
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.8	48.1	49.8
standard deviation	± 11.00	± 11.80	± 11.04
Gender categorical Units: Subjects			
Male	17	39	25
Female	15	24	19
Ethnicity Units: Subjects			
Hispanic or Latino	1	3	0
Not Hispanic or Latino	25	40	26
Unknown or Not Reported	6	20	18
Race Units: Subjects			
Asian	4	4	1
Black or African American	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	1
White	22	37	23
Not Reported	6	20	18
Other	0	1	1

Reporting group values	Total		
Number of subjects	139		
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Male	81		
Female	58		
Ethnicity Units: Subjects			
Hispanic or Latino	4		
Not Hispanic or Latino	91		
Unknown or Not Reported	44		
Race Units: Subjects			
Asian	9		
Black or African American	1		
Native Hawaiian or Other Pacific Islander	1		
White	82		
Not Reported	44		
Other	2		

End points

End points reporting groups

Reporting group title	233AS101: Part C (Prior Placebo)

Reporting group description:

Participants who were randomized to placebo in Part C of the parent study 233AS101 received 3 loading doses of BIIB067, 100mg, Q2W, on Days 1, 15, and 29 by IT bolus injection in this study followed by up to 90 maintenance doses of BIIB067, Q4W, until the last enrolled participant had their Week 152 maintenance dose visit.

Reporting group title	233AS101: Part C (Prior BIIB067 100 mg)

Reporting group description:

Participants who were randomized to BIIB067 100 mg in Part C of the parent study 233AS101 received 2 loading doses of BIIB067, 100 mg, on Days 1 and 29, and one dose of BIIB067-matched placebo on Day 15 by IT bolus injection in this study followed by up to 90 maintenance doses of BIIB067,Q4W, until the last enrolled participant had their Week 152 maintenance dose visit.

Reporting group title	233AS101: Part A and B (All doses)

Reporting group description:

Participants who were randomized to BIIB067 or placebo in Part A (at doses 10 mg, 20 mg, 40 mg and 60 mg) or Part B (at doses 20 mg, 40 mg, 60 mg and 100 mg) of the parent study 233AS101 received 3 loading doses of BIIB067, 20 mg, 40 mg, 60 mg, or 100 mg, eventually escalated to 100 mg, 2 weeks apart, and up to 90 maintenance doses, Q4W, by IT bolus injection until the last enrolled participant had their Week 152 maintenance dose visit in this study.

Subject analysis set title	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who were randomized to placebo in Part C of the parent study 233AS101 received 3 loading doses of BIIB067, 100 mg, Q2W, on Days 1, 15, and 29 by IT bolus injection in this study followed by up to 90 maintenance doses of BIIB067, Q4W, until the last enrolled participant had their Week 152 maintenance dose visit.

Subject analysis set title	233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who were randomized to BIIB067 100 mg in Part C of the parent study 233AS101 received 2 loading doses of BIIB067, 100 mg, on Days 1 and 29, and one dose of BIIB067-matched placebo on Day 15 by IT bolus injection in this study followed by up to 90 maintenance doses of BIIB067,Q4W, until the last enrolled participant had their Week 152 maintenance dose visit.

Primary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious AEs (TESAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious AEs (TESAEs) [1]

End point description:

AE: any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product & that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable & unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. An SAE is any untoward medical occurrence that at any dose results in death, life-threatening event, requires inpatient hospitalization, significant disability/incapacity or congenital anomaly. TEAEs were defined as any AE or SAE with an onset date & time that was on or after the first dose of study drug, or any pre-existing condition that worsened in severity after the first dose of study drug. Safety population included all participants who were enrolled and received at least one dose of study treatment in 233AS102.

End point type	Primary

End point timeframe:

From first dose of the study drug in the current study up to end of follow-up period (up to Week 364)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned for this endpoint.

End point values	233AS101: Part C (Prior Placebo)	233AS101: Part C (Prior BIIB067 100 mg)	233AS101: Part A and B (All doses)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	63	44	
Units: participants				
TEAEs	31	63	43	
TESAEs	16	33	22	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of BIIB067

End point title	Plasma Concentration of BIIB067 [2]

End point description:

As planned, the plasma concentration of BIIB067 was summarised for 233AS101 Part C participants only. The pharmacokinetic (PK) population included all participants who received at least 1 dose of study treatment and had at least 1 post-dosing PK concentration measurement. 'Subjects analysed' signifies the number of participants evaluable for this outcome measure at the specified time point.

End point type	Secondary

End point timeframe:

Week 4

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Part C arms were planned to be analysed for this end point.

End point values	233AS101: Part C (Prior Placebo)	233AS101: Part C (Prior BIIB067 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	60		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard error)				
Week 4	1.22 (± 0.118)	2.05 (± 0.516)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of BIIB067 in Cerebrospinal Fluid (CSF)

End point title	Concentration of BIIB067 in Cerebrospinal Fluid (CSF) [3]

End point description:

As planned, the CSF concentration of BIIB067 was summarised for 233AS101 Part C participants only. The PK population included all participants who received at least 1 dose of study treatment and had at least 1 post-dosing PK concentration measurement. 'Subjects analysed' signifies number of participants evaluable for this outcome measure at the specified timepoint.

End point type	Secondary

End point timeframe:

Week 4

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Part C arms were planned to be analysed for this end point.

End point values	233AS101: Part C (Prior Placebo)	233AS101: Part C (Prior BIIB067 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	47		
Units: ng/mL				
arithmetic mean (standard error)				
Week 4	19.35 (± 2.829)	9.18 (± 0.711)		

Statistical analyses

No statistical analyses for this end point

Secondary: 233AS101 and 233AS102 Integrated Summary of Efficacy (ISE): Total CSF Superoxide Dismutase 1 (SOD1) Protein Ratio to Baseline

End point title	233AS101 and 233AS102 Integrated Summary of Efficacy (ISE): Total CSF Superoxide Dismutase 1 (SOD1) Protein Ratio to Baseline

End point description:

This endpoint as not a standalone analysis for 233AS102. Analysis was performed on the data collected from both 233AS101 and 233AS102 studies. This is reported as a part of the final integrated analyses. Baseline is defined as the Day 1 of 233AS101 Part C. Data has been reported for Weeks 52, 104 and 148 from the 233AS101 Part C baseline. Integrated analysis was performed on overall ITT population which included all Part C subjects of 233AS101 and subjects who rolled over from 233AS101 Part C into 233AS102. 'Subjects analysed' exceeds total number of subjects who started 233AS102 as it indicates subjects randomised in Part C of 233AS101 study. Number analyzed 'n' indicates the number of subjects evaluable for this endpoint at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 52, 104 and 148

End point values	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg	233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	72		
Units: ratio				
geometric mean (confidence interval 95%)				
Week 52 (n = 25, 52)	0.78 (0.64 to 0.96)	0.67 (0.57 to 0.79)		
Week 104 (n = 17, 44)	0.81 (0.67 to 0.97)	0.74 (0.65 to 0.84)		
Week 148 (n = 11, 41)	0.75 (0.61 to 0.92)	0.79 (0.69 to 0.91)		

Statistical analyses

Statistical analysis title	Week 52

Statistical analysis description:

The analysis was based on an analysis of covariance (ANCOVA) model with natural log transformed data. The model included covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone. Multiple imputation (MI) including treatment group, use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least square (LS) geometric mean ratio
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.08

Statistical analysis title	Week 148

Statistical analysis description:

The analysis was based on an ANCOVA model with natural log transformed data. The model included covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6344 [4]
Method	ANCOVA
Parameter estimate	LS geometric mean ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.34

Notes:

[4] - ANCOVA model using MI.

Statistical analysis title	Week 104

Statistical analysis description:

The analysis was based on an ANCOVA model with natural log transformed data. The model included covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3711 [5]
Method	ANCOVA
Parameter estimate	LS geometric mean ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.11

Notes:

[5] - ANCOVA model using MI.

Secondary: 233AS101 and 233AS102 ISE: Neurofilament Light Chain (NfL) Plasma Concentration Ratio to Baseline

End point title	233AS101 and 233AS102 ISE: Neurofilament Light Chain (NfL) Plasma Concentration Ratio to Baseline

End point description:

This endpoint was not a standalone analysis for 233AS102. Analysis was performed on the data collected from both 233AS101 and 233AS102 studies. This is reported as a part of the final integrated analyses. Baseline is defined as the Day 1 of 233AS101 Part C. Data has been reported for Weeks 52, 104 and 148 from the 233AS101 Part C baseline. Integrated analysis was performed on overall ITT population which included all Part C subjects of 233AS101 and subjects who rolled over from 233AS101 Part C into 233AS102. 'Subjects analysed' exceeds total number of subjects who started 233AS102 as it indicates subjects randomised in Part C of 233AS101 study. Number analyzed 'n' indicates the number of subjects evaluable for this endpoint at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 52, 104 and 148

End point values	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg	233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	72		
Units: ratio				
geometric mean (confidence interval 95%)				
Week 52 (n = 23, 50)	0.62 (0.49 to 0.78)	0.50 (0.42 to 0.60)		
Week 104 (n = 18, 42)	0.41 (0.30 to 0.55)	0.33 (0.27 to 0.42)		
Week 148 (n = 11, 41)	0.36 (0.25 to 0.53)	0.33 (0.26 to 0.43)		

Statistical analyses

Statistical analysis title	Week 52

Statistical analysis description:

The analysis was based on an ANCOVA model with natural log transformed data. The model included covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS geometric mean ratio
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.03

Statistical analysis title	Week 104

Statistical analysis description:

The analysis was based on an ANCOVA model with natural log transformed data. The model included covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2306 [6]
Method	ANCOVA
Parameter estimate	LS geometric mean ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.13

Notes:

[6] - ANCOVA model using MI.

Statistical analysis title	Week 148

Statistical analysis description:

The analysis was based on an ANCOVA model with natural log transformed data. The model included covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.673 [7]
Method	ANCOVA
Parameter estimate	LS geometric mean ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.38

Notes:

[7] - ANCOVA model using MI.

Secondary: 233AS101 and 233AS102 ISE: Change From Baseline in Total Amyotropic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) Score

End point title	233AS101 and 233AS102 ISE: Change From Baseline in Total Amyotropic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) Score

End point description:

ALSFRS-R measures 4 functional domains-respiratory, bulbar function, gross motor skills,& fine motor skills. There are 12 questions, each scored from 0 (no function) to 4 (full function).ALSFRS-R total score= sum of 4 functional domain scores, ranging from 0 to 48, where higher scores=better function. Negative change from baseline=disease progression. This endpoint was not a standalone analysis for 233AS102. Analysis was performed on data collected from 233AS101 & 233AS102 studies. This is reported as a part of final integrated analyses. Baseline=Day 1 of 233AS101 Part C. Data reported for Weeks 52, 104& 148 from 233AS101 Part C baseline. Integrated analysis was performed on overall ITT

population. 'Subjects analysed' exceeds total number of subjects who started 233AS102 as it indicates subjects randomised in Part C of 233AS101 study. Number analyzed 'n' indicates the number of subjects evaluable for this endpoint at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 52, 104 and 148

End point values	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg	233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	72		
Units: score on a scale				
least squares mean (standard error)				
Week 52 (n=28, 57)	-9.5 (± 1.46)	-5.9 (± 1.16)		
Week 104 (n=20, 49)	-13.1 (± 2.12)	-9.4 (± 1.69)		
Week 148 (n=13, 46)	-13.5 (± 2.28)	-9.9 (± 1.77)		

Statistical analyses

Statistical analysis title	Week 52

Statistical analysis description:

The analysis was based on an ANCOVA model that included treatment as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, baseline NfL, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	6.7
Variability estimate	Standard error of the mean
Dispersion value	1.58

Statistical analysis title	Week 148

Statistical analysis description:

The analysis was based on an ANCOVA model that included treatment as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, baseline NfL, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1432 [8]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	8.4
Variability estimate	Standard error of the mean
Dispersion value	2.46

Notes:

[8] - ANCOVA model using MI.

Statistical analysis title	Week 104

Statistical analysis description:

The analysis was based on an ANCOVA model that included treatment as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, baseline NfL, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1054 [9]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	8.2
Variability estimate	Standard error of the mean
Dispersion value	2.28

Notes:

[9] - ANCOVA model using MI.

Secondary: 233AS101 and 233AS102 ISE: Change From Baseline in Percent Predicted Slow Vital Capacity (SVC)

End point title	233AS101 and 233AS102 ISE: Change From Baseline in Percent Predicted Slow Vital Capacity (SVC)

End point description:

Vital capacity was measured by means of SVC test, administered in upright position. Upright SVC was determined by performing 3 to 5 measures, per criteria established by American Thoracic Society &European Respiratory Society. Percent predicted SVC=[observed SVC/predicted SVC]*100%. Predicted SVC was adjusted by sex, age, height, programmed into & performed by equipment used. Negative change from baseline=worsening of respiratory capacity. This endpoint was not standalone analysis for 233AS102. Analysis was performed on data collected from 233AS101& 233AS102 studies. This is reported as part of final integrated analyses. Baseline=Day 1 of 233AS101 Part C. Data has been reported for Weeks 52,104 & 148 from 233AS101 Part C baseline.Integrated analysis performed on overall ITT population. 'Subjects analysed' exceeds number of subjects started 233AS102 as it indicates subjects randomised in Part C of 233AS101. Number analyzed 'n'=number of subjects evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 52, 104 and 148

End point values	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg	233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	72		
Units: percentage of predicted volume				
least squares mean (standard error)				
Week 52 (n = 20, 38)	-18.7 (± 3.70)	-10.6 (± 2.99)		
Week 104 (n = 10, 31)	-23.7 (± 5.90)	-14.4 (± 4.46)		
Week 148 (n = 10, 32)	-18.1 (± 5.74)	-13.8 (± 4.07)		

Statistical analyses

Statistical analysis title	Week 52

Statistical analysis description:

The analysis was based on an ANCOVA model that included treatment as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline percent predicted SVC and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, baseline NfL, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference
Point estimate	8.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	15.9
Variability estimate	Standard error of the mean
Dispersion value	3.99

Statistical analysis title	Week 104

Statistical analysis description:

The analysis was based on an ANCOVA model that included treatment as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline percent predicted SVC and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, baseline NfL, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0963 [10]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	9.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	20.4
Variability estimate	Standard error of the mean
Dispersion value	5.6

Notes:

[10] - ANCOVA model using MI.

Statistical analysis title	Week 148

Statistical analysis description:

The analysis was based on an ANCOVA model that included treatment as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline percent predicted SVC and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, baseline NfL, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4388 [11]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	4.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	15.2
Variability estimate	Standard error of the mean
Dispersion value	5.56

Notes:

[11] - ANCOVA model using MI.

Secondary: 233AS101 and 233AS102 ISE: Change From Baseline in Handheld Dynamometry (HHD) Overall Megascore

End point title	233AS101 and 233AS102 ISE: Change From Baseline in Handheld Dynamometry (HHD) Overall Megascore

End point description:

Quantitative muscle strength was evaluated using HHD Megascore, which tests isometric strength of multiple muscles using standard participant positioning. Approximately 8 muscle groups were examined (per each side) in both upper & lower extremities. Muscle strength values were normalized to Z scores as (post-baseline measurements-mean)/SD & averaged to provide HHD overall megascore. Overall megascore was created by averaging all eight bilateral measurement Z scores, if no more than 10 (≤ 10) measures are missing. Negative change from baseline= decreased muscle strength. This endpoint was not a standalone analysis for 233AS102. Analysis was performed on data collected from 233AS101 & 233AS102 studies. This is reported as part of final integrated analyses. Baseline=Day 1 of 233AS101 Part C. Data has been reported for Weeks 52, 104 & 148 from 233AS101 Part C baseline. Integrated analysis was performed on overall ITT population (all Part C 233AS101 subjects & rolled over Part C subjects)

End point type	Secondary

End point timeframe:

Baseline, Weeks 52, 104 and 148

End point values	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg	233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	72		
Units: score on a scale				
least squares mean (standard error)				
Week 52 (n = 25, 42)	-0.41 (± 0.101)	-0.15 (± 0.079)		
Week 104 (n = 10, 32)	-0.56 (± 0.154)	-0.42 (± 0.112)		
Week 148 (n = 10, 36)	-0.43 (± 0.089)	-0.38 (± 0.062)		

Statistical analyses

Statistical analysis title	Week 52

Statistical analysis description:

The analysis was based on an ANCOVA model that included treatment as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline HHD overall megascore and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, baseline NfL, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.477
Variability estimate	Standard error of the mean
Dispersion value	0.109

Statistical analysis title	Week 104

Statistical analysis description:

The analysis was based on an ANCOVA model that included treatment as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline HHD overall megascore and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, baseline NfL, and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3207 [12]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.141
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.145

Notes:

[12] - ANCOVA model using MI.

Statistical analysis title	Week 148

Statistical analysis description:

The analysis was based on an ANCOVA model that included treatment as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline HHD overall megascore and use of riluzole or edaravone. Multiple imputation including treatment group, use of riluzole or edaravone, baseline NfL,

and the relevant baseline and postbaseline values for the endpoint was used for missing data.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5452 [13]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.124
upper limit	0.234
Variability estimate	Standard error of the mean
Dispersion value	0.091

Notes:

[13] - ANCOVA model using MI.

Secondary: 233AS101 and 233AS102 ISE: Change From Baseline in Individual Muscle Strength Assessed by HHD

End point title	233AS101 and 233AS102 ISE: Change From Baseline in Individual Muscle Strength Assessed by HHD

End point description:

Individual muscle strength was evaluated using handheld dynamometer, which tests the isometric strength of multiple muscles using standard participant positioning. Eight muscle groups were examined (per each side) in both upper and lower extremities. Negative change from baseline indicated decreased muscle strength. This outcome measure was not a standalone analysis for 233AS102. Analysis was performed on data collected from both 233AS101 & 233AS102 studies. This is reported as a part of final integrated analyses. Baseline=Day 1 of 233AS101 Part C. Data is reported for Weeks 52, 104&148 from 233AS101 Part C baseline. The analyses was based on observed data. Integrated analysis was performed on overall ITT population. 'Subjects analysed' exceeds number of subjects who started 233AS102 as it indicates subjects randomised in Part C of 233AS101 study. 'n'=the number of subjects evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 52, 104 and 148

End point values	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg	233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	72		
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Left Shoulder Flexion: Week 52 (n = 25, 41)	-3.42 (± 6.671)	-0.51 (± 8.484)		
Left Shoulder Flexion: Week 104 (n = 10, 32)	0.17 (± 5.714)	-4.16 (± 14.329)		

Left Shoulder Flexion: Week 148 (n = 10, 36)	-2.48 (± 5.075)	-4.12 (± 8.543)		
Left Elbow Flexion: Week 52 (n = 25, 42)	-3.89 (± 6.747)	-0.24 (± 8.031)		
Left Elbow Flexion: Week 104 (n = 10, 32)	-1.26 (± 7.361)	-3.12 (± 13.334)		
Left Elbow Flexion: Week 148 (n = 10, 36)	0.65 (± 4.560)	-3.33 (± 8.753)		
Left Wrist Extension: Week 52 (n = 25, 41)	-3.66 (± 4.775)	-0.41 (± 7.170)		
Left Wrist Extension: Week 104 (n = 10, 32)	-0.86 (± 5.279)	-1.74 (± 8.517)		
Left Wrist Extension: Week 148 (n = 10, 36)	0.95 (± 5.242)	-2.49 (± 6.086)		
Lt.AbductionIndex1stDorsalInterosseous Wk52n=25,42	-0.96 (± 1.450)	-0.93 (± 4.448)		
Lt.AbductionIndex1stDorsalInterosseos Wk104n=10,32	-0.63 (± 1.266)	-0.62 (± 2.279)		
Lt.AbductionIndex1stDorsalInterosseos Wk148n=10,36	-0.41 (± 1.604)	-1.28 (± 4.913)		
Lt.AbductionThumbAbductorPollicusBrvis Wk52n=25,41	-1.15 (± 1.486)	-0.70 (± 2.497)		
LtAbductionThumbAbductorPollicusBrvis Wk104n=10,32	-0.69 (± 1.089)	-0.19 (± 2.382)		
LtAbductionThumbAbductorPollicusBrvis Wk148n=10,36	-1.10 (± 2.324)	-0.78 (± 3.049)		
LtAbduction5thDigitAbductorDigitiMiniWk52n=25,41	-0.66 (± 1.208)	-0.49 (± 2.296)		
LtAbduction5thDigitAbductorDigitiMiniWk104n=10,31	-0.47 (± 1.226)	-0.50 (± 1.999)		
LtAbduction5thDigitAbductorDigitiMiniWk148n=10,36	-0.43 (± 1.496)	-0.66 (± 2.394)		
Left Knee Extension: Week 52 (n = 25, 42)	-4.94 (± 8.015)	1.80 (± 10.744)		
Left Knee Extension: Week 104 (n = 10, 32)	-2.41 (± 6.545)	-1.54 (± 13.222)		
Left Knee Extension: Week 148 (n = 10, 35)	-2.48 (± 7.339)	-2.01 (± 9.711)		
Left Ankle Dorsiflexion: Week 52 (n = 25, 42)	-2.82 (± 7.560)	0.72 (± 7.701)		
Left Ankle Dorsiflexion: Week 104 (n = 10, 31)	-5.47 (± 3.590)	-4.20 (± 11.516)		
Left Ankle Dorsiflexion: Week 148 (n = 10, 35)	-5.43 (± 5.303)	-2.33 (± 9.533)		
Right Shoulder Flexion: Week 52 (n = 25, 41)	-4.74 (± 5.494)	-0.96 (± 5.728)		
Right Shoulder Flexion: Week 104 (n = 10, 32)	-2.72 (± 4.638)	-2.81 (± 9.304)		
Right Shoulder Flexion: Week 148 (n = 10, 36)	-3.02 (± 5.066)	-3.18 (± 8.139)		
Right Elbow Flexion: Week 52 (n = 25, 41)	-4.03 (± 5.663)	-1.20 (± 7.015)		
Right Elbow Flexion: Week 104 (n = 10, 31)	-1.32 (± 6.289)	-3.04 (± 9.717)		
Right Elbow Flexion: Week 148 (n = 10, 35)	0.49 (± 3.407)	-3.28 (± 8.704)		
Right Wrist Extension: Week 52 (n = 25, 42)	-3.82 (± 5.892)	-0.63 (± 4.870)		

Right Wrist Extension: Week 104 (n = 10, 32)	-0.76 (± 4.086)	-1.65 (± 6.267)		
Right Wrist Extension: Week 148 (n = 10, 36)	0.09 (± 5.096)	-1.89 (± 5.033)		
Rt.AbductionIndex1stDorsalInterosseosWk52n=25,42	-0.86 (± 1.381)	-0.36 (± 1.405)		
Rt.AbductionIndex1stDorsalInterosseosWk104n=10,31	-0.38 (± 1.057)	-0.45 (± 1.569)		
Rt.AbductionIndex1stDorsalInterosseosWk148n=10,36	-0.23 (± 1.545)	-0.46 (± 1.193)		
Rt.AbductionThumbAbductorPollicusBrvisWk52n=25,41	-0.98 (± 1.425)	-1.24 (± 4.595)		
RtAbductionThumbAbductorPollicusBrvisWk104n=10,32	-0.31 (± 0.947)	-0.24 (± 2.016)		
RtAbductionThumbAbductorPollicusBrvisWk148n=10,36	-0.86 (± 1.861)	-1.10 (± 5.247)		
RtAbduction5thDigitAbductorDigitiMiniWk52n=25,41	-0.78 (± 1.210)	-1.12 (± 5.112)		
RtAbduction5thDigitAbductorDigitiMiniWk104n=10,31	-0.54 (± 1.059)	-0.21 (± 1.639)		
RtAbduction5thDigitAbductorDigitiMiniWk148n=10,36	-0.69 (± 1.009)	-1.36 (± 5.634)		
Right Knee Extension: Week 52 (n = 25, 42)	-4.90 (± 5.964)	1.05 (± 8.973)		
Right Knee Extension: Week 104 (n = 10, 32)	-2.16 (± 9.453)	-3.09 (± 13.046)		
Right Knee Extension: Week 148 (n = 10, 35)	-0.19 (± 7.407)	-1.60 (± 7.685)		
Right Ankle Dorsiflexion: Week 52 (n = 25, 42)	-5.68 (± 8.907)	-1.05 (± 5.923)		
Right Ankle Dorsiflexion: Week 104 (n = 10, 32)	-5.86 (± 3.501)	-3.78 (± 13.008)		
Right Ankle Dorsiflexion: Week 148 (n = 10, 36)	-6.74 (± 7.308)	-3.40 (± 8.172)		

Statistical analyses

No statistical analyses for this end point

Secondary: 233AS101 and 233AS102 ISE: Time to Death or Permanent Ventilation

End point title	233AS101 and 233AS102 ISE: Time to Death or Permanent Ventilation

End point description:

Permanent ventilation: ≥ 22 hours of mechanical ventilation [invasive /noninvasive] per day for ≥ 21 consecutive days. Event of permanent ventilation based on an adjudicated event (i.e., adjudicated by Endpoint Adjudication Committee (EAC) as having met permanent ventilation criteria defined in protocol). Time to death or permanent ventilation=time to earliest occurrence of death/permanent ventilation. Start date for calculating time to death or permanent ventilation in days=date of first dose. Subjects without event were censored at last known alive dates. This endpoint not standalone analysis for 233AS102.Analysis performed on data collected from 233AS101 &233AS102 studies. This is reported as part of final integrated analyses. Overall ITT population. Subjects analysed exceeds total number of subjects who started 233AS102 as it indicates subjects who were randomised in Part C of 233AS101 study. '9999' means due to low number of events, median & upper range of 95% CI not estimable.

End point type	Secondary

End point timeframe:

From the baseline of the study 233AS101 up to the end of the follow-up period of the current study (up to Week 364)

End point values	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg	233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	72		
Units: weeks				
median (confidence interval 95%)	9999 (135.6 to 9999)	9999 (253.6 to 9999)		

Statistical analyses

Statistical analysis title	Time to Death or Permanent Ventilation

Statistical analysis description:

Time to Death or Permanent Ventilation was summarized using the Kaplan-Meier product limit method.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4202 [14]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.282
upper limit	1.461

Notes:

[14] - The analysis was based on a log rank test stratified by median baseline plasma NfL.

Secondary: 233AS101 and 233AS102 ISE: Time to Death

End point title	233AS101 and 233AS102 ISE: Time to Death

End point description:

Time to death was defined as time from first dose received in 233AS101 to death. Subjects who do not meet the endpoint definition were censored at the subject’s last known alive date. Only events that were adjudicated by the EAC are included. This endpoint was not a standalone analysis for 233AS102. Analysis was performed on the data collected from 233AS101 and 233AS102 studies. This is reported as a part of the final integrated analyses. Time to death was summarized using the Kaplan-Meier product limit method. Integrated analysis was performed on overall ITT population which included all Part C participants of 233AS101 and participants who rolled over from 233AS101 Part C into 233AS102. 'Subjects analysed' exceeds the total number of participants who started 233AS102 as it indicates participants who were randomised in the Part C of 233AS101 study. '9999' signifies that due to the low

number of events, the median and 95% CI were not estimable.

End point type	Secondary

End point timeframe:

From the baseline of the study 233AS101 up to the end of the follow-up period of the current study (up to Week 364)

End point values	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg	233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	72		
Units: weeks				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (260.7 to 9999)		

Statistical analyses

Statistical analysis title	Time to Death

Statistical analysis description:

Time to death was summarized using the Kaplan-Meier product limit method.

Comparison groups	233AS101&233AS102(Part C):Placebo+Delayed-start BIIB067 100mg v 233AS101 & 233AS102 (Part C): Early-start BIIB067 100 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3108 [15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.199
upper limit	1.357

Notes:

[15] - The analysis was based on a log rank test stratified by median baseline plasma NfL.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of the study drug in the current study up to end of follow-up period (up to Week 364)

Adverse event reporting additional description:

The safety population included all participants who were enrolled and received at least one dose of study treatment in 233AS102.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	233AS101: Part C (Prior Placebo)

Reporting group description:

Participants who were randomised to placebo in Part C of the parent study 233AS101 received 3 loading doses of BIIB067, 100 mg, Q2W, on Days 1, 15, and 29 by IT bolus injection in this study followed by up to 90 maintenance doses of BIIB067, Q4W, until the last participant enrolled had their Week 152 maintenance dose visit.

Reporting group title	233AS101: Parts A and B (All Doses)

Reporting group description:

Participants who were randomized to BIIB067 or placebo in Part A (at doses 10 mg, 20 mg, 40 mg and 60 mg) or Part B (at doses 20 mg, 40 mg, 60 mg and 100 mg) of the parent study 233AS101 received 3 loading doses of BIIB067, 20 mg, 40 mg, 60 mg, or 100 mg, eventually escalated to 100 mg, 2 weeks apart, and up to 90 maintenance doses, Q4W, by IT bolus injection until the last enrolled participant had their Week 152 maintenance dose visit in this study.

Reporting group title	233AS101: Part C (Prior BIIB067 100 mg)

Reporting group description:

Participants who were randomised to BIIB067, 100 mg in Part C of the parent study 233AS101 received 2 loading doses of BIIB067, 100 mg on Days 1 and 29, and one dose of BIIB067-matched placebo on Day 15 by IT bolus injection in this study followed by up to 90 maintenance doses of BIIB067, Q4W, until the last participant enrolled had their Week 152 maintenance dose visit.

Serious adverse events	233AS101: Part C (Prior Placebo)	233AS101: Parts A and B (All Doses)	233AS101: Part C (Prior BIIB067 100 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 32 (50.00%)	22 / 44 (50.00%)	33 / 63 (52.38%)
number of deaths (all causes)	7	5	14
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer recurrent			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cancer			

subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Euthanasia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Death			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	6 / 63 (9.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Aspiration			

subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagobronchial fistula			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis aspiration			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 32 (0.00%)	2 / 44 (4.55%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			

subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pulmonary embolism			
subjects affected / exposed	2 / 32 (6.25%)	2 / 44 (4.55%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	6 / 32 (18.75%)	5 / 44 (11.36%)	6 / 63 (9.52%)
occurrences causally related to treatment / all	0 / 6	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 6	0 / 2	0 / 4
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal behaviour			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Staphylococcus test positive			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fall			
subjects affected / exposed	0 / 32 (0.00%)	4 / 44 (9.09%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Atrial fibrillation			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myopericarditis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Brain hypoxia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Encephalopathy			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	1 / 32 (3.13%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	1 / 32 (3.13%)	1 / 44 (2.27%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuromyelitis optica spectrum disorder			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurosarcoidosis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	1 / 32 (3.13%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 32 (3.13%)	3 / 44 (6.82%)	7 / 63 (11.11%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer perforation			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral disc protrusion			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 32 (3.13%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
H1n1 influenza			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19 pneumonia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 44 (2.27%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pharyngeal abscess			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			

subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelitis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 44 (2.27%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	3 / 32 (9.38%)	2 / 44 (4.55%)	8 / 63 (12.70%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Pneumonia bacterial			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyelonephritis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Staphylococcal infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 32 (3.13%)	1 / 44 (2.27%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	233AS101: Part C (Prior Placebo)	233AS101: Parts A and B (All Doses)	233AS101: Part C (Prior BIIB067 100 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 32 (96.88%)	43 / 44 (97.73%)	63 / 63 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 32 (3.13%)	7 / 44 (15.91%)	3 / 63 (4.76%)
occurrences (all)	1	8	4

Hypotension			
subjects affected / exposed	1 / 32 (3.13%)	0 / 44 (0.00%)	4 / 63 (6.35%)
occurrences (all)	1	0	5
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	2 / 32 (6.25%)	5 / 44 (11.36%)	2 / 63 (3.17%)
occurrences (all)	2	7	2
Fatigue			
subjects affected / exposed	10 / 32 (31.25%)	13 / 44 (29.55%)	16 / 63 (25.40%)
occurrences (all)	10	26	31
Chills			
subjects affected / exposed	1 / 32 (3.13%)	5 / 44 (11.36%)	5 / 63 (7.94%)
occurrences (all)	1	11	5
Malaise			
subjects affected / exposed	2 / 32 (6.25%)	2 / 44 (4.55%)	0 / 63 (0.00%)
occurrences (all)	15	2	0
Vaccination site pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	4 / 63 (6.35%)
occurrences (all)	0	1	5
Pyrexia			
subjects affected / exposed	8 / 32 (25.00%)	11 / 44 (25.00%)	11 / 63 (17.46%)
occurrences (all)	84	26	13
Peripheral swelling			
subjects affected / exposed	2 / 32 (6.25%)	5 / 44 (11.36%)	3 / 63 (4.76%)
occurrences (all)	4	5	3
Pain			
subjects affected / exposed	3 / 32 (9.38%)	2 / 44 (4.55%)	5 / 63 (7.94%)
occurrences (all)	4	2	8
Oedema peripheral			
subjects affected / exposed	2 / 32 (6.25%)	6 / 44 (13.64%)	3 / 63 (4.76%)
occurrences (all)	2	8	9
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 32 (3.13%)	2 / 44 (4.55%)	5 / 63 (7.94%)
occurrences (all)	1	3	7
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 32 (9.38%)	6 / 44 (13.64%)	5 / 63 (7.94%)
occurrences (all)	3	13	6
Dyspnoea			
subjects affected / exposed	3 / 32 (9.38%)	5 / 44 (11.36%)	11 / 63 (17.46%)
occurrences (all)	3	5	17
Laryngospasm			
subjects affected / exposed	0 / 32 (0.00%)	2 / 44 (4.55%)	4 / 63 (6.35%)
occurrences (all)	0	4	6
Nasal congestion			
subjects affected / exposed	1 / 32 (3.13%)	5 / 44 (11.36%)	4 / 63 (6.35%)
occurrences (all)	1	6	4
Oropharyngeal pain			
subjects affected / exposed	2 / 32 (6.25%)	6 / 44 (13.64%)	5 / 63 (7.94%)
occurrences (all)	2	9	6
Rhinorrhoea			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	4 / 63 (6.35%)
occurrences (all)	0	1	5
Sinus congestion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	4 / 63 (6.35%)
occurrences (all)	0	1	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 32 (3.13%)	3 / 44 (6.82%)	6 / 63 (9.52%)
occurrences (all)	1	4	7
Depression			
subjects affected / exposed	0 / 32 (0.00%)	5 / 44 (11.36%)	5 / 63 (7.94%)
occurrences (all)	0	5	5
Insomnia			
subjects affected / exposed	3 / 32 (9.38%)	5 / 44 (11.36%)	6 / 63 (9.52%)
occurrences (all)	4	5	8
Panic attack			
subjects affected / exposed	0 / 32 (0.00%)	3 / 44 (6.82%)	1 / 63 (1.59%)
occurrences (all)	0	5	1
Investigations			

Csf protein increased			
subjects affected / exposed	7 / 32 (21.88%)	15 / 44 (34.09%)	15 / 63 (23.81%)
occurrences (all)	7	19	16
Csf glucose increased			
subjects affected / exposed	0 / 32 (0.00%)	2 / 44 (4.55%)	4 / 63 (6.35%)
occurrences (all)	0	3	4
Blood urine present			
subjects affected / exposed	0 / 32 (0.00%)	4 / 44 (9.09%)	2 / 63 (3.17%)
occurrences (all)	0	4	2
Alanine aminotransferase increased			
subjects affected / exposed	2 / 32 (6.25%)	2 / 44 (4.55%)	4 / 63 (6.35%)
occurrences (all)	2	2	5
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 32 (0.00%)	2 / 44 (4.55%)	4 / 63 (6.35%)
occurrences (all)	0	2	5
Blood glucose increased			
subjects affected / exposed	1 / 32 (3.13%)	4 / 44 (9.09%)	2 / 63 (3.17%)
occurrences (all)	1	4	4
Csf white blood cell count increased			
subjects affected / exposed	2 / 32 (6.25%)	11 / 44 (25.00%)	15 / 63 (23.81%)
occurrences (all)	2	15	16
White blood cell count increased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 44 (2.27%)	4 / 63 (6.35%)
occurrences (all)	0	1	4
Oxygen saturation decreased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences (all)	2	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 32 (0.00%)	3 / 44 (6.82%)	3 / 63 (4.76%)
occurrences (all)	0	3	3
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 32 (3.13%)	4 / 44 (9.09%)	1 / 63 (1.59%)
occurrences (all)	2	5	1
Fall			

subjects affected / exposed	18 / 32 (56.25%)	28 / 44 (63.64%)	25 / 63 (39.68%)
occurrences (all)	35	120	94
Contusion			
subjects affected / exposed	7 / 32 (21.88%)	13 / 44 (29.55%)	8 / 63 (12.70%)
occurrences (all)	9	18	13
Post procedural complication			
subjects affected / exposed	0 / 32 (0.00%)	3 / 44 (6.82%)	0 / 63 (0.00%)
occurrences (all)	0	7	0
Post lumbar puncture syndrome			
subjects affected / exposed	6 / 32 (18.75%)	13 / 44 (29.55%)	15 / 63 (23.81%)
occurrences (all)	21	123	90
Neurological procedural complication			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	4 / 63 (6.35%)
occurrences (all)	2	0	4
Muscle strain			
subjects affected / exposed	1 / 32 (3.13%)	5 / 44 (11.36%)	3 / 63 (4.76%)
occurrences (all)	3	5	3
Ligament sprain			
subjects affected / exposed	1 / 32 (3.13%)	4 / 44 (9.09%)	3 / 63 (4.76%)
occurrences (all)	1	7	3
Immunisation reaction			
subjects affected / exposed	1 / 32 (3.13%)	5 / 44 (11.36%)	2 / 63 (3.17%)
occurrences (all)	3	7	4
Head injury			
subjects affected / exposed	2 / 32 (6.25%)	2 / 44 (4.55%)	1 / 63 (1.59%)
occurrences (all)	2	2	1
Post procedural contusion			
subjects affected / exposed	3 / 32 (9.38%)	2 / 44 (4.55%)	2 / 63 (3.17%)
occurrences (all)	4	2	2
Post procedural pruritus			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences (all)	2	0	0
Post procedural swelling			
subjects affected / exposed	0 / 32 (0.00%)	4 / 44 (9.09%)	1 / 63 (1.59%)
occurrences (all)	0	5	1
Procedural nausea			

subjects affected / exposed	0 / 32 (0.00%)	2 / 44 (4.55%)	4 / 63 (6.35%)
occurrences (all)	0	8	5
Procedural pain			
subjects affected / exposed	14 / 32 (43.75%)	28 / 44 (63.64%)	33 / 63 (52.38%)
occurrences (all)	48	216	264
Skin abrasion			
subjects affected / exposed	1 / 32 (3.13%)	6 / 44 (13.64%)	4 / 63 (6.35%)
occurrences (all)	1	7	14
Skin laceration			
subjects affected / exposed	1 / 32 (3.13%)	3 / 44 (6.82%)	3 / 63 (4.76%)
occurrences (all)	1	6	3
Traumatic lumbar puncture			
subjects affected / exposed	0 / 32 (0.00%)	3 / 44 (6.82%)	0 / 63 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	2 / 32 (6.25%)	4 / 44 (9.09%)	2 / 63 (3.17%)
occurrences (all)	2	4	2
Burning sensation			
subjects affected / exposed	1 / 32 (3.13%)	3 / 44 (6.82%)	1 / 63 (1.59%)
occurrences (all)	1	4	1
Dizziness			
subjects affected / exposed	5 / 32 (15.63%)	13 / 44 (29.55%)	13 / 63 (20.63%)
occurrences (all)	10	29	18
Dysarthria			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	4 / 63 (6.35%)
occurrences (all)	2	0	5
Intracranial pressure increased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	4 / 63 (6.35%)
occurrences (all)	2	0	4
Hypoaesthesia			
subjects affected / exposed	4 / 32 (12.50%)	5 / 44 (11.36%)	2 / 63 (3.17%)
occurrences (all)	6	9	2
Headache			
subjects affected / exposed	17 / 32 (53.13%)	31 / 44 (70.45%)	35 / 63 (55.56%)
occurrences (all)	72	157	195

Migraine			
subjects affected / exposed	1 / 32 (3.13%)	4 / 44 (9.09%)	2 / 63 (3.17%)
occurrences (all)	1	9	2
Paraesthesia			
subjects affected / exposed	3 / 32 (9.38%)	5 / 44 (11.36%)	7 / 63 (11.11%)
occurrences (all)	4	10	22
Muscle spasticity			
subjects affected / exposed	2 / 32 (6.25%)	2 / 44 (4.55%)	3 / 63 (4.76%)
occurrences (all)	3	17	33
Muscle contractions involuntary			
subjects affected / exposed	2 / 32 (6.25%)	4 / 44 (9.09%)	6 / 63 (9.52%)
occurrences (all)	2	4	9
Tremor			
subjects affected / exposed	2 / 32 (6.25%)	4 / 44 (9.09%)	1 / 63 (1.59%)
occurrences (all)	2	4	3
Sensory disturbance			
subjects affected / exposed	2 / 32 (6.25%)	1 / 44 (2.27%)	1 / 63 (1.59%)
occurrences (all)	16	4	1
Sciatica			
subjects affected / exposed	0 / 32 (0.00%)	3 / 44 (6.82%)	2 / 63 (3.17%)
occurrences (all)	0	4	2
Radicular pain			
subjects affected / exposed	1 / 32 (3.13%)	3 / 44 (6.82%)	0 / 63 (0.00%)
occurrences (all)	1	4	0
Pleocytosis			
subjects affected / exposed	3 / 32 (9.38%)	7 / 44 (15.91%)	5 / 63 (7.94%)
occurrences (all)	3	11	5
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 32 (0.00%)	5 / 44 (11.36%)	3 / 63 (4.76%)
occurrences (all)	0	6	4
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences (all)	2	0	0
Papilloedema			

subjects affected / exposed	2 / 32 (6.25%)	1 / 44 (2.27%)	3 / 63 (4.76%)
occurrences (all)	2	1	5
Dry eye			
subjects affected / exposed	1 / 32 (3.13%)	3 / 44 (6.82%)	0 / 63 (0.00%)
occurrences (all)	1	4	0
Vision blurred			
subjects affected / exposed	2 / 32 (6.25%)	1 / 44 (2.27%)	3 / 63 (4.76%)
occurrences (all)	3	2	4
Diplopia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences (all)	2	0	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 32 (9.38%)	4 / 44 (9.09%)	3 / 63 (4.76%)
occurrences (all)	4	8	4
Abdominal distension			
subjects affected / exposed	2 / 32 (6.25%)	1 / 44 (2.27%)	2 / 63 (3.17%)
occurrences (all)	2	1	2
Abdominal pain			
subjects affected / exposed	1 / 32 (3.13%)	4 / 44 (9.09%)	5 / 63 (7.94%)
occurrences (all)	1	5	6
Abdominal discomfort			
subjects affected / exposed	0 / 32 (0.00%)	4 / 44 (9.09%)	1 / 63 (1.59%)
occurrences (all)	0	4	1
Constipation			
subjects affected / exposed	10 / 32 (31.25%)	11 / 44 (25.00%)	12 / 63 (19.05%)
occurrences (all)	11	16	13
Diarrhoea			
subjects affected / exposed	12 / 32 (37.50%)	7 / 44 (15.91%)	7 / 63 (11.11%)
occurrences (all)	18	7	10
Nausea			
subjects affected / exposed	7 / 32 (21.88%)	17 / 44 (38.64%)	13 / 63 (20.63%)
occurrences (all)	20	41	36
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 32 (0.00%)	4 / 44 (9.09%)	8 / 63 (12.70%)
occurrences (all)	0	4	9

Dysphagia			
subjects affected / exposed	1 / 32 (3.13%)	3 / 44 (6.82%)	7 / 63 (11.11%)
occurrences (all)	1	8	9
Dyspepsia			
subjects affected / exposed	2 / 32 (6.25%)	3 / 44 (6.82%)	2 / 63 (3.17%)
occurrences (all)	3	4	3
Salivary hypersecretion			
subjects affected / exposed	1 / 32 (3.13%)	2 / 44 (4.55%)	13 / 63 (20.63%)
occurrences (all)	1	3	14
Toothache			
subjects affected / exposed	0 / 32 (0.00%)	4 / 44 (9.09%)	3 / 63 (4.76%)
occurrences (all)	0	4	3
Vomiting			
subjects affected / exposed	2 / 32 (6.25%)	7 / 44 (15.91%)	3 / 63 (4.76%)
occurrences (all)	2	9	3
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	3 / 32 (9.38%)	0 / 44 (0.00%)	2 / 63 (3.17%)
occurrences (all)	3	0	2
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 32 (3.13%)	3 / 44 (6.82%)	0 / 63 (0.00%)
occurrences (all)	1	3	0
Decubitus ulcer			
subjects affected / exposed	2 / 32 (6.25%)	1 / 44 (2.27%)	1 / 63 (1.59%)
occurrences (all)	2	1	4
Erythema			
subjects affected / exposed	2 / 32 (6.25%)	2 / 44 (4.55%)	0 / 63 (0.00%)
occurrences (all)	2	2	0
Pruritus			
subjects affected / exposed	2 / 32 (6.25%)	1 / 44 (2.27%)	3 / 63 (4.76%)
occurrences (all)	10	2	4
Urticaria			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	0 / 63 (0.00%)
occurrences (all)	2	0	0
Rash			

subjects affected / exposed	2 / 32 (6.25%)	6 / 44 (13.64%)	6 / 63 (9.52%)
occurrences (all)	3	7	9
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 32 (3.13%)	5 / 44 (11.36%)	2 / 63 (3.17%)
occurrences (all)	1	5	2
Nephrolithiasis			
subjects affected / exposed	3 / 32 (9.38%)	3 / 44 (6.82%)	3 / 63 (4.76%)
occurrences (all)	3	9	3
Micturition urgency			
subjects affected / exposed	0 / 32 (0.00%)	3 / 44 (6.82%)	0 / 63 (0.00%)
occurrences (all)	0	3	0
Haematuria			
subjects affected / exposed	0 / 32 (0.00%)	3 / 44 (6.82%)	1 / 63 (1.59%)
occurrences (all)	0	3	1
Dysuria			
subjects affected / exposed	2 / 32 (6.25%)	1 / 44 (2.27%)	1 / 63 (1.59%)
occurrences (all)	2	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 32 (37.50%)	17 / 44 (38.64%)	19 / 63 (30.16%)
occurrences (all)	26	41	43
Back pain			
subjects affected / exposed	14 / 32 (43.75%)	26 / 44 (59.09%)	27 / 63 (42.86%)
occurrences (all)	35	83	59
Joint swelling			
subjects affected / exposed	3 / 32 (9.38%)	3 / 44 (6.82%)	5 / 63 (7.94%)
occurrences (all)	3	3	5
Muscle spasms			
subjects affected / exposed	8 / 32 (25.00%)	11 / 44 (25.00%)	11 / 63 (17.46%)
occurrences (all)	12	21	19
Muscle twitching			
subjects affected / exposed	1 / 32 (3.13%)	1 / 44 (2.27%)	4 / 63 (6.35%)
occurrences (all)	1	1	5
Muscular weakness			

subjects affected / exposed	5 / 32 (15.63%)	4 / 44 (9.09%)	10 / 63 (15.87%)
occurrences (all)	5	10	34
Musculoskeletal chest pain			
subjects affected / exposed	2 / 32 (6.25%)	5 / 44 (11.36%)	3 / 63 (4.76%)
occurrences (all)	2	5	4
Musculoskeletal pain			
subjects affected / exposed	1 / 32 (3.13%)	7 / 44 (15.91%)	3 / 63 (4.76%)
occurrences (all)	17	10	12
Musculoskeletal stiffness			
subjects affected / exposed	1 / 32 (3.13%)	6 / 44 (13.64%)	4 / 63 (6.35%)
occurrences (all)	1	101	4
Myalgia			
subjects affected / exposed	4 / 32 (12.50%)	12 / 44 (27.27%)	14 / 63 (22.22%)
occurrences (all)	4	45	40
Neck pain			
subjects affected / exposed	3 / 32 (9.38%)	6 / 44 (13.64%)	5 / 63 (7.94%)
occurrences (all)	4	6	7
Pain in extremity			
subjects affected / exposed	12 / 32 (37.50%)	19 / 44 (43.18%)	17 / 63 (26.98%)
occurrences (all)	43	78	44
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 32 (3.13%)	6 / 44 (13.64%)	3 / 63 (4.76%)
occurrences (all)	1	8	5
Cellulitis			
subjects affected / exposed	0 / 32 (0.00%)	4 / 44 (9.09%)	1 / 63 (1.59%)
occurrences (all)	0	4	1
Covid-19			
subjects affected / exposed	7 / 32 (21.88%)	13 / 44 (29.55%)	26 / 63 (41.27%)
occurrences (all)	11	17	34
Cystitis			
subjects affected / exposed	3 / 32 (9.38%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences (all)	3	0	4
Gastroenteritis viral			
subjects affected / exposed	0 / 32 (0.00%)	4 / 44 (9.09%)	3 / 63 (4.76%)
occurrences (all)	0	4	3

Influenza			
subjects affected / exposed	1 / 32 (3.13%)	4 / 44 (9.09%)	3 / 63 (4.76%)
occurrences (all)	1	4	4
Lower respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	4 / 44 (9.09%)	2 / 63 (3.17%)
occurrences (all)	1	11	3
Nasopharyngitis			
subjects affected / exposed	6 / 32 (18.75%)	20 / 44 (45.45%)	11 / 63 (17.46%)
occurrences (all)	13	41	17
Oral candidiasis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	2 / 63 (3.17%)
occurrences (all)	2	0	2
Oral herpes			
subjects affected / exposed	0 / 32 (0.00%)	4 / 44 (9.09%)	0 / 63 (0.00%)
occurrences (all)	0	5	0
Pneumonia			
subjects affected / exposed	3 / 32 (9.38%)	5 / 44 (11.36%)	4 / 63 (6.35%)
occurrences (all)	3	5	5
Pneumonia aspiration			
subjects affected / exposed	2 / 32 (6.25%)	0 / 44 (0.00%)	3 / 63 (4.76%)
occurrences (all)	3	0	4
Rhinitis			
subjects affected / exposed	3 / 32 (9.38%)	1 / 44 (2.27%)	2 / 63 (3.17%)
occurrences (all)	5	1	2
Sinusitis			
subjects affected / exposed	4 / 32 (12.50%)	3 / 44 (6.82%)	4 / 63 (6.35%)
occurrences (all)	6	8	5
Suspected covid-19			
subjects affected / exposed	2 / 32 (6.25%)	1 / 44 (2.27%)	1 / 63 (1.59%)
occurrences (all)	2	1	1
Tooth infection			
subjects affected / exposed	0 / 32 (0.00%)	3 / 44 (6.82%)	1 / 63 (1.59%)
occurrences (all)	0	4	2
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	4 / 44 (9.09%)	0 / 63 (0.00%)
occurrences (all)	0	4	0

Viral infection			
subjects affected / exposed	1 / 32 (3.13%)	4 / 44 (9.09%)	1 / 63 (1.59%)
occurrences (all)	1	7	1
Urinary tract infection			
subjects affected / exposed	5 / 32 (15.63%)	12 / 44 (27.27%)	8 / 63 (12.70%)
occurrences (all)	12	22	14
Upper respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	9 / 44 (20.45%)	7 / 63 (11.11%)
occurrences (all)	0	11	13
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 32 (6.25%)	2 / 44 (4.55%)	2 / 63 (3.17%)
occurrences (all)	2	3	2
Decreased appetite			
subjects affected / exposed	3 / 32 (9.38%)	0 / 44 (0.00%)	1 / 63 (1.59%)
occurrences (all)	3	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2017	Eliminated the requirement to review data from Day 106 through Day 169 of Study 233AS101 before dosing the first and second subject enrolling in each cohort of Study 233AS102. Clarified criteria for enrolling subjects who complete only Part A of Study 233AS101. A condition under which subjects may be rescreened was added.
12 March 2018	Extend the treatment period by 12 months for all participants in the study. Added a fourth treatment group of BIIB067 100 mg. Removed anti-BIIB067 antibody sampling from the Screening Visit. Included information on edaravone as a current therapy for ALS. Added description of a 9-month nonclinical toxicology study in cynomolgus monkeys (NHPs). Deleted laboratory assessments, vital signs, and physical examinations from the primary endpoint. The number of sites participating in this study was decreased to 16. Changes were made describing the process for participants switching to a higher-dose cohort. An eligibility criterion was added specifying the 16-week washout prior to the participant's first dose in this study. In addition, an eligibility criterion was updated to permit the use of edaravone provided it is not administered on dosing days. Updates were made to the exclusion criteria for hepatitis C- and B. In addition, presence of implanted venous devices was added as an exclusion criterion. The types of neurological examinations to be conducted at study sites were added. Coagulation assessments were separated from other hematology assessments. Text was added stating that participants will be informed about the collection of race and ethnicity data.
11 January 2019	Extend the study duration that allowed any and all participants to receive treatment until either the participant's Final Visit at Week 248 or until the last subject randomised has had his or her Week 92 Visit, whichever occurs first. The phase of development was updated to accurately reflect the need of the long-term extension study. Study rationale text was updated with the evaluation of PD, PK, and effect of disease progression of BIIB067. Updated the dose for all participants in Study 233AS102 to 100 mg BIIB067. Clarified that study objectives were being assessed in subjects with ALS and confirmed SOD1 mutation. The secondary objective was updated to include disease progression. As a result, the ALSFRS-R scores, SVC, and HHD scores exploratory endpoints were changed to secondary endpoints, and the VAFS and overall survival were added as secondary endpoints. Deleted uncontrolled from the study design, and allowed participation of participants who have completed Part C of Study 233AS101; added text for all participants who have completed Parts A, B, or C of Study 233AS101 to receive 100 mg BIIB067, regardless of their treatment dose in Study 233AS101 or prior dosing in Study 233AS102; and specified that participants who have completed Part C of Study 233AS101 do not need to undergo a washout period but are required to undergo a loading dose period. Inclusion and exclusion criteria were updated to align with Part C of Study 233AS101 and as per study requirements. Clarified that the loading dose will occur during the first 4 weeks of treatment and that the Maintenance Dose Period will be extended to approximately 58 doses. Details of the prior dosing regimen were removed. The sample size was increased from 84 to 144 participants. Added an independent data monitoring committee (IDMC) and removed the reference to the Safety Surveillance Team (SST).

08 November 2019	Updated the secondary endpoints to include; revised the definition of HHD and ventilation assistance-free survival (VAFS) secondary endpoints. Statistical methodology was updated to allow the analysis of efficacy using the change from baseline. Sample size was increased from 144 to 183 participants. Exclusion criterion 1, excluding participants with current or prior hepatitis B infection, and exclusion criterion 8, excluding the presence of an implanted intravenous port/catheter were removed. Section 13.4, Genomic and Pharmacogenomic Assessments, was added. Change describing the "effects on disease progression of BIIB067" was updated throughout to "efficacy of BIIB067. Study Overview, was updated with the total number of countries and number of planned sites globally and to clarify that the last Maintenance Dose Visit for participants will occur at Week 236 OR when the last participant enrolled has had his or her Week 92 Maintenance Dose Visit, whichever occurs first. Dosing section, was updated to clarify that Day 1 of this study should occur no earlier than 28 days after the participant's last dose (i.e., Day 169 [Week 24 Visit]) in Study 233AS101 to prevent participants from being dosed too soon. Analysis Population section, was updated to remove the requirement that participants must have at least 1 available postdosing evaluation of the respective clinical function endpoint to be included in the analysis population.
04 August 2021	Extended the maintenance dosing portion of the treatment period of the study by up to 124 weeks while minimizing the burden on participants. Information on the duration of BIIB067 administration was added. Consistent with Study 233AS101, the protocol was revised to reflect that plasma NfL will be evaluated as a secondary biomarker endpoint. The time-to-event endpoints were renamed so that VAFS was relabeled as time to death or permanent ventilation, and overall survival was renamed as time to death. The efficacy endpoint was updated to change over time in total ALSFRS-R scores. The PD endpoint was updated to change from baseline in SOD1 protein in CSF. References to the last study visit from Part C of Study 233AS101 were updated since either Week 28 or Week 32 Visit could be considered the End of Study Visit. A clarification was added to describe procedures for adverse events (AEs) that are ongoing when the participant completes or discontinues the study. A clarification was added to state that serious AEs (SAEs) are to be recorded on an SAE form (instead of the case report form [CRF]) and must be reported to the Sponsor according to national law (in addition to the prespecified timeframe). Details on the analysis population were expanded to include relevant information on the integrated analyses of the 233AS101 and 233AS102 studies, as well as clarification on the subgroup analysis for 233AS102 alone. Details on the analysis of covariance and Kaplan-Meier curves were clarified. References to "dose level" in the descriptions of analyses were removed and replaced with more general identifiers such as "treatment group" or removed entirely. The summary of the analyses was also revised to reflect the key statistical estimates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported