Clinical trial results:
A Multicenter, Double-Blind, Multidose, Placebo-Controlled, Randomized, Parallel-Group, Phase 2 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 for Patients With Brain Contusion

Summary

EudraCT number	2018-003858-24
Trial protocol	ES IT
Global end of trial date	27 June 2023

Results information

Result version number	v1 (current)
This version publication date	15 December 2023
First version publication date	15 December 2023

Trial information

Trial identification

Sponsor protocol code	252BN201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03954041
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen 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	27 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 June 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine if BIIB093 reduces brain contusion expansion by Hour 96 when compared to placebo. The secondary objectives were to evaluate the effects of BIIB093 on acute neurologic status, functional outcomes, and treatment requirements, to further differentiate the mechanism of action of BIIB093 on contusion expansion by examining differential effects on hematoma and edema expansion, and to determine if BIIB093 improves survival at Day 90 when compared to placebo.

Protection of trial subjects:

Written informed consent was obtained from each participant or participant's legally authorized representative (e.g., legal guardian), as applicable, prior to evaluations performed for eligibility. Participants or the participant's legally authorized representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2019
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	Spain: 21
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Israel: 2
Worldwide total number of subjects	86
EEA total number of subjects	51

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)	54
From 65 to 84 years	31
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study centers in Israel, France, Japan, Italy, Spain, and the United States.

Pre-assignment

Screening details:

A total of 92 participants were enrolled and randomized, out of which 86 participants were dosed with BIIB093 or a matching placebo.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants were administered with BIIB093 matching placebo as an intravenous (IV) bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BIIB093 matching placebo administered as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.

Arm title	BIIB093 3 mg/day

Arm description:

Participants were administered with BIIB093 up to 3 milligrams per day (mg/day) as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.

Arm type	Experimental
Investigational medicinal product name	BIIB093
Investigational medicinal product code	
Other name	Glibenclamide, CIRARA, RP 1127
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Up to 3mg/day BIIB093 administered as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.

Arm title	BIIB093 5 mg/day

Arm description:

Participants were administered with BIIB093 up to 5 mg/day as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.

Arm type	Experimental

Investigational medicinal product name	BIIB093
Investigational medicinal product code	
Other name	Glibenclamide, CIRARA, RP 1127
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Up to 5mg/day BIIB093 administered as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.

Number of subjects in period 1	Placebo	BIIB093 3 mg/day	BIIB093 5 mg/day
Started	44	21	21
Completed	30	14	11
Not completed	14	7	10
Adverse event, serious fatal	4	-	1
Other	7	4	2
Lost to follow-up	3	3	6
Death by neurologic criteria	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants were administered with BIIB093 matching placebo as an intravenous (IV) bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.	
Reporting group title	BIIB093 3 mg/day
Reporting group description:	
Participants were administered with BIIB093 up to 3 milligrams per day (mg/day) as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.	
Reporting group title	BIIB093 5 mg/day
Reporting group description:	
Participants were administered with BIIB093 up to 5 mg/day as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.	

Reporting group values	Placebo	BIIB093 3 mg/day	BIIB093 5 mg/day
Number of subjects	44	21	21
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.3	55.7	55.0
standard deviation	± 14.18	± 19.87	± 21.02
Gender categorical Units: Subjects			
Male	36	18	18
Female	8	3	3
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	4
Not Hispanic or Latino	39	15	14
Not Reported	3	4	3
Race Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	12	5	5
Black or African American	1	0	0
White	26	12	13
Not Reported	2	4	3
Other	2	0	0

Reporting group values	Total		
Number of subjects	86		
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Male	72		
Female	14		
Ethnicity Units: Subjects			
Hispanic or Latino	8		
Not Hispanic or Latino	68		
Not Reported	10		
Race Units: Subjects			
American Indian or Alaska Native	1		
Asian	22		
Black or African American	1		
White	51		
Not Reported	9		
Other	2		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants were administered with BIIB093 matching placebo as an intravenous (IV) bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.	
Reporting group title	BIIB093 3 mg/day
Reporting group description:	
Participants were administered with BIIB093 up to 3 milligrams per day (mg/day) as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.	
Reporting group title	BIIB093 5 mg/day
Reporting group description:	
Participants were administered with BIIB093 up to 5 mg/day as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.	

Primary: Change From Baseline in Mean Total Contusion Volume (Hematoma Plus Perihematomal Edema) at 96 Hours as Measured by Brain Imaging

End point title	Change From Baseline in Mean Total Contusion Volume (Hematoma Plus Perihematomal Edema) at 96 Hours as Measured by Brain Imaging

End point description:

Total contusion volume including hematoma and perihematomal edema volumes reported in mL was assessed by the central imaging core laboratory on baseline non-contrast computed tomography (NCCT), 24-hour NCCT, and the 96-hour scan (Magnetic resonance imaging [MRI and/or NCCT) and the scans obtained prior to decompressive craniectomy (DC), intraparenchymal hematoma (IPH) evacuation, or comfort measures only (CMO). Modified intent to treat (mITT) population included all randomised participants who received any study drug (BIIB093 or placebo) and had at least one final read per central review of contusion volume from a NCCT or MRI scan acquired between 10 hours after initiation of study drug infusion and Hour 96 visit or neurosurgical intervention (NSx) or CMO, if earlier. Here, 'subjects analysed' signifies number of participants with data available for endpoint analysis. 'Number analysed (n)' signifies number of participants with data available for analysis at specified timepoint.

End point type	Primary

End point timeframe:

Baseline up to 96 hours (Day 4)

End point values	Placebo	BIIB093 3 mg/day	BIIB093 5 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	20	19	
Units: milliliters (mL)				
arithmetic mean (standard deviation)				
Baseline (n=38,20, 19)	29.45 (± 29.688)	21.21 (± 26.659)	21.33 (± 26.637)	
Change From Baseline at 96 hours (n=34,19,15)	18.91 (± 23.804)	30.07 (± 29.418)	18.78 (± 12.771)	

Statistical analyses

Statistical analysis title	Combined BIIB093 vs Placebo
Comparison groups	Placebo v BIIB093 3 mg/day v BIIB093 5 mg/day
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3752 [1]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	4.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.74
upper limit	14.98

Notes:

[1] - P-value was analyzed by ANCOVA model with covariates: treatment, interactive response technology (IRT) stratification factors at randomization, baseline total contusion volume based on central read, imaging modality at Hour 96 (MRI vs NCCT).

Secondary: Percentage of Participants With Glasgow Outcome Scale - Extended (GOS-E) Score at Day 180

End point title	Percentage of Participants With Glasgow Outcome Scale - Extended (GOS-E) Score at Day 180

End point description:

The GOS-E is a global scale for functional outcomes that rates participant status on a 7-category ordinal scale into one of five categories: 1 and 2: Dead and Vegetative State, 3 and 4: Severe disability lower and upper categories, 5 and 6: Moderate disability lower and upper categories, 7 and 8: Good recovery lower and upper categories. Lower scores indicate death and higher scores indicate recovery. mITT population included all the randomised participants who received any study drug (BIIB093 or placebo) and had at least one final read per central review of contusion volume from a NCCT or MRI scan acquired between 10 hours after the initiation of study drug infusion and the Hour 96 visit or NSx or CMO, if earlier. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis.

End point type	Secondary

End point timeframe:

Day 180

End point values	Placebo	BIIB093 3 mg/day	BIIB093 5 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	15	11	
Units: percentage of participants				
number (not applicable)				
Score: 1/2	0	0	0	
Score: 3	13.3	13.3	27.3	
Score: 4	0	26.7	9.1	
Score: 5	13.3	6.7	0	
Score: 6	26.7	0	0	
Score: 7	6.7	13.3	27.3	
Score: 8	40.0	40.0	36.4	

Statistical analyses

Statistical analysis title	Combined BIIB093 vs Placebo
Comparison groups	Placebo v BIIB093 3 mg/day v BIIB093 5 mg/day
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.36

Secondary: Percentage of Participants With Modified Rankin Scale (mRS) Score at Day 90

End point title	Percentage of Participants With Modified Rankin Scale (mRS) Score at Day 90

End point description:

The mRS measures the degree of disability or dependence in the daily activities of participants who had suffered a stroke or other causes of neurological disability on a 5-category ordinal scale: 0/1, 2, 3, 4, 5/6. Lower scores indicate perfect health without symptoms and higher scores indicate death. mITT population included all the randomised participants who received any study drug (BIIB093 or placebo) and had at least one final read per central review of contusion volume from a NCCT or MRI scan acquired between 10 hours after the initiation of study drug infusion and the Hour 96 visit or NSx or CMO, if earlier. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis.

End point type	Secondary

End point timeframe:

Day 90

End point values	Placebo	BIIB093 3 mg/day	BIIB093 5 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	19	14	
Units: percentage of participants				
number (not applicable)				
Score: 0/1	38.5	31.6	57.1	
Score: 2	25.6	26.3	7.1	
Score: 3	12.8	21.1	0	
Score: 4	10.3	15.8	21.4	
Score: 5/6	12.8	5.3	14.3	

Statistical analyses

Statistical analysis title	Combined BIIB093 vs Placebo
Comparison groups	Placebo v BIIB093 3 mg/day v BIIB093 5 mg/day
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4306 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	3.86

Notes:

[2] - P-value was analysed by ordinal logistic regression on mRS adjusting for covariates: treatment, IRT stratification factors at randomisation, baseline GCS based on eCRF, baseline mRS score, and baseline total contusion volume based on central read.

Secondary: Percentage of Participants Requiring Delayed Intubation

End point title	Percentage of Participants Requiring Delayed Intubation

End point description:

Delayed intubation is defined as participants requiring intubation (for neurologic deterioration only) at any time between 24 hours and 96 hours post-injury. mITT population included all the randomised participants who received any study drug (BIIB093 or placebo) and had at least one final read per central review of contusion volume from a NCCT or MRI scan acquired between 10 hours after the initiation of study drug infusion and the Hour 96 visit or NSx or CMO, if earlier.

End point type	Secondary

End point timeframe:

Day 1 (24 hours) up to Day 4 (96 hours) post-injury

End point values	Placebo	BIIB093 3 mg/day	BIIB093 5 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	21	20	
Units: percentage of participants				
number (not applicable)	2.3	4.8	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Total Contusion Volume (Hematoma Plus Perihematomal Edema) to 24 Hours as Measured by Brain Imaging

End point title	Change From Baseline in Mean Total Contusion Volume (Hematoma Plus Perihematomal Edema) to 24 Hours as Measured by Brain Imaging

End point description:

Total contusion volume including hematoma and perihematomal edema volumes reported in mL was assessed by the central imaging core laboratory on baseline NCCT, 24-hour NCCT. mITT population included all the randomised participants who received any study drug (BIIB093 or placebo) and had at least one final read per central review of contusion volume from a NCCT or MRI scan acquired between 10 hours after the initiation of study drug infusion and the Hour 96 visit or NSx or CMO, if earlier. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis. 'Number analysed (n)' signifies the number of participants with data available for analysis at a specified timepoint.

End point type	Secondary

End point timeframe:

Baseline up to 24 hours (Day 1)

End point values	Placebo	BIIB093 3 mg/day	BIIB093 5 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	20	19	
Units: mL				
arithmetic mean (standard deviation)				
Baseline (n=38, 20, 19)	29.45 (± 29.688)	21.21 (± 26.659)	21.33 (± 26.637)	
Change From Baseline at 24 hours (n= 36, 19, 18)	8.16 (± 18.824)	11.24 (± 13.909)	6.67 (± 13.483)	

Statistical analyses

Statistical analysis title	Combined BIIB093 vs Placebo
Comparison groups	Placebo v BIIB093 3 mg/day v BIIB093 5 mg/day
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6478 [3]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.19
upper limit	5.13

Notes:

[3] - P-value was analyzed by ANCOVA model with covariates: treatment, IRT stratification factors at randomization, baseline total contusion volume based on central read.

Secondary: Change From Baseline in Absolute Hematoma Volume at 24 Hours

End point title	Change From Baseline in Absolute Hematoma Volume at 24 Hours

End point description:

Hematoma volume reported in mL was assessed by the central imaging core laboratory on baseline NCCT, 24-hour NCCT, and the scans obtained prior to DC, IPH evacuation, or CMO. mITT population included all the randomised participants who received any study drug (BIIB093 or placebo) and had at least one final read per central review of contusion volume from a NCCT or MRI scan acquired between 10 hours after the initiation of study drug infusion and the Hour 96 visit or NSx or CMO, if earlier. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis. 'Number analysed (n)' signifies the number of participants with data available for analysis at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline up to 24 hours (Day 1)

End point values	Placebo	BIIB093 3 mg/day	BIIB093 5 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	20	20	
Units: mL				
arithmetic mean (standard deviation)				
Baseline (n=40, 20, 20)	6.72 (± 10.012)	6.11 (± 12.086)	3.62 (± 3.737)	
Change From Baseline at 24 hours (n=38, 19, 19)	2.07 (± 5.920)	2.13 (± 3.667)	2.23 (± 3.537)	

Statistical analyses

Statistical analysis title	Combined BIIB093 vs Placebo
Comparison groups	Placebo v BIIB093 3 mg/day v BIIB093 5 mg/day
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9314 [4]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	2.02

Notes:

[4] - P-value was analyzed by ANCOVA model with covariates: treatment, IRT stratification factors at randomization, baseline Glasgow Coma Scale (GCS) based on eCRF, and baseline absolute hematoma volume based on central read.

Secondary: Change From Baseline in Absolute Edema Volume at 96 Hours

End point title	Change From Baseline in Absolute Edema Volume at 96 Hours

End point description:

Edema volume reported in mL was assessed by the central imaging core laboratory on baseline NCCT, 24-hour NCCT, and the 96-hour scan (MRI and/or NCCT) and the scans obtained prior to DC, IPH evacuation, or CMO. mITT population included all the randomised participants who received any study drug (BIIB093 or placebo) and had at least one final read per central review of contusion volume from a NCCT or MRI scan acquired between 10 hours after the initiation of study drug infusion and the Hour 96 visit or NSx or CMO, if earlier. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis. 'Number analysed (n)' signifies the number of participants with data available for analysis at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline up to 96 hours (Day 4)

End point values	Placebo	BIIB093 3 mg/day	BIIB093 5 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	20	19	
Units: mL				
arithmetic mean (standard deviation)				
Baseline (n=38, 20, 19)	22.41 (± 23.234)	15.10 (± 16.366)	17.52 (± 24.103)	
Change From Baseline at 96 hours (n=34, 19, 15)	16.13 (± 20.872)	25.87 (± 27.772)	14.98 (± 10.459)	

Statistical analyses

Statistical analysis title	Combined BIIB093 vs Placebo
Comparison groups	Placebo v BIIB093 3 mg/day v BIIB093 5 mg/day
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6569 [5]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.61
upper limit	11.98

Notes:

[5] - P-value was analyzed by ANCOVA model with covariates: treatment, IRT stratification factors at randomization, baseline absolute edema volume based on central read, baseline GCS based on eCRF, and imaging modality at Hour 96 (MRI vs NCCT).

Secondary: Time to All-Cause Death Through Day 90

End point title	Time to All-Cause Death Through Day 90

End point description:

Time to all-cause death is defined as the time from randomisation to the time of death and includes all-cause death along with neurological death. mITT population included all the randomised participants who received any study drug (BIIB093 or placebo) and had at least one final read per central review of contusion volume from a NCCT or MRI scan acquired between 10 hours after the initiation of study drug infusion and the Hour 96 visit or NSx or CMO, if earlier. Here, 'subjects analysed' signifies the number of participants who died from randomisation up to Day 90. 9999=Not estimable due to the small number of deaths.

End point type	Secondary

End point timeframe:

Randomisation up to Day 90

End point values	Placebo	BIIB093 3 mg/day	BIIB093 5 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	0[6]	1	
Units: days				
median (inter-quartile range (Q1-Q3))	9999 (9999 to 9999)	(to)	9999 (9999 to 9999)	

Notes:

[6] - Zero deaths were observed in this arm group.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent up to last follow-up visit (approximately 1360 days)

Adverse event reporting additional description:

Safety analysis set included all randomized participants who had received any infusion of the study drug (BIIB093 or placebo).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants were administered with BIIB093 matching placebo as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.

Reporting group title	BIIB093 5mg/day

Reporting group description:

Participants were administered with BIIB093 up to 5 mg/day as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.

Reporting group title	BIIB093 3mg/day

Reporting group description:

Participants were administered with BIIB093 up to 3 mg/day as an IV bolus followed by a rapid IV infusion and a slow IV infusion for 4 days.

Serious adverse events	Placebo	BIIB093 5mg/day	BIIB093 3mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 44 (27.27%)	8 / 19 (42.11%)	7 / 23 (30.43%)
number of deaths (all causes)	4	2	0
number of deaths resulting from adverse events	4	2	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (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
Clavicle fracture			
subjects affected / exposed	0 / 44 (0.00%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			

subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (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
Subdural haematoma			
subjects affected / exposed	2 / 44 (4.55%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 44 (0.00%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 44 (0.00%)	0 / 19 (0.00%)	1 / 23 (4.35%)
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			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	0 / 23 (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
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Cerebral haemorrhage			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (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
Epilepsy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	2 / 44 (4.55%)	3 / 19 (15.79%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Neurological decompensation			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (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
Gastrointestinal disorders			
Rectal haemorrhage			

subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (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			
Cholecystitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (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
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (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
Apnoea			
subjects affected / exposed	0 / 44 (0.00%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Restlessness			
subjects affected / exposed	0 / 44 (0.00%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Korsakoff's syndrome			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (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
Infections and infestations			
Pneumonia staphylococcal			

subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (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
Klebsiella sepsis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (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
Urosepsis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	0 / 23 (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
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 44 (0.00%)	4 / 19 (21.05%)	4 / 23 (17.39%)
occurrences causally related to treatment / all	0 / 0	4 / 4	4 / 4
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	Placebo	BIIB093 5mg/day	BIIB093 3mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 44 (81.82%)	18 / 19 (94.74%)	20 / 23 (86.96%)
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 44 (13.64%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences (all)	8	0	1
Hypertension			
subjects affected / exposed	9 / 44 (20.45%)	4 / 19 (21.05%)	6 / 23 (26.09%)
occurrences (all)	9	4	6
Phlebitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Orthostatic hypotension			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	4 / 44 (9.09%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	4	0	0
Generalised oedema			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Asthenia			
subjects affected / exposed	2 / 44 (4.55%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	2	0	2
Medical device site erosion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	9 / 44 (20.45%)	3 / 19 (15.79%)	6 / 23 (26.09%)
occurrences (all)	10	3	6
Oedema peripheral			
subjects affected / exposed	2 / 44 (4.55%)	1 / 19 (5.26%)	2 / 23 (8.70%)
occurrences (all)	3	2	2
Reproductive system and breast disorders			

Priapism			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Respiratory alkalosis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Respiratory acidosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	3 / 44 (6.82%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences (all)	3	0	1
Atelectasis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 44 (6.82%)	0 / 19 (0.00%)	3 / 23 (13.04%)
occurrences (all)	3	0	3
Disorientation			
subjects affected / exposed	3 / 44 (6.82%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	3	0	0
Delirium			
subjects affected / exposed	1 / 44 (2.27%)	3 / 19 (15.79%)	1 / 23 (4.35%)
occurrences (all)	1	3	1
Confusional state			
subjects affected / exposed	2 / 44 (4.55%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	2	1	1
Agitation			
subjects affected / exposed	6 / 44 (13.64%)	3 / 19 (15.79%)	1 / 23 (4.35%)
occurrences (all)	6	3	1
Irritability			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Restlessness			

subjects affected / exposed	0 / 44 (0.00%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Investigations			
C-reactive protein increased			
subjects affected / exposed	6 / 44 (13.64%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	6	0	2
Electroencephalogram abnormal			
subjects affected / exposed	3 / 44 (6.82%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences (all)	3	0	1
Fibrin d dimer increased			
subjects affected / exposed	4 / 44 (9.09%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	4	0	2
Haemoglobin decreased			
subjects affected / exposed	2 / 44 (4.55%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	2	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 44 (11.36%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	5	0	0
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Bradycardia			
subjects affected / exposed	5 / 44 (11.36%)	2 / 19 (10.53%)	4 / 23 (17.39%)
occurrences (all)	5	2	4
Atrial fibrillation			
subjects affected / exposed	3 / 44 (6.82%)	1 / 19 (5.26%)	2 / 23 (8.70%)
occurrences (all)	3	1	2
Tachycardia			
subjects affected / exposed	3 / 44 (6.82%)	1 / 19 (5.26%)	2 / 23 (8.70%)
occurrences (all)	3	1	2
Nervous system disorders			

Altered state of consciousness			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Anosmia			
subjects affected / exposed	3 / 44 (6.82%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	3	0	2
Aphasia			
subjects affected / exposed	2 / 44 (4.55%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	7	0	4
Cognitive disorder			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2
Dementia with lewy bodies			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	3 / 44 (6.82%)	2 / 19 (10.53%)	1 / 23 (4.35%)
occurrences (all)	3	2	1
Epilepsy			
subjects affected / exposed	3 / 44 (6.82%)	1 / 19 (5.26%)	2 / 23 (8.70%)
occurrences (all)	3	1	2
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Syncope			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Subdural hygroma			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2
Seizure			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0

Neurological decompensation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	3 / 44 (6.82%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences (all)	3	0	1
Lateral medullary syndrome			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Lacunar infarction			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Intracranial pressure increased			
subjects affected / exposed	5 / 44 (11.36%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	5	1	0
Headache			
subjects affected / exposed	7 / 44 (15.91%)	2 / 19 (10.53%)	4 / 23 (17.39%)
occurrences (all)	7	2	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 44 (11.36%)	2 / 19 (10.53%)	2 / 23 (8.70%)
occurrences (all)	5	2	2
Dilutional anaemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2
Eye disorders			
Anisocoria			
subjects affected / exposed	3 / 44 (6.82%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	6	0	0
Vision blurred			

subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 44 (9.09%)	1 / 19 (5.26%)	5 / 23 (21.74%)
occurrences (all)	4	1	5
Salivary hypersecretion			
subjects affected / exposed	4 / 44 (9.09%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences (all)	4	0	1
Proctitis haemorrhagic			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	3 / 44 (6.82%)	3 / 19 (15.79%)	1 / 23 (4.35%)
occurrences (all)	3	3	1
Dysphagia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Diarrhoea			
subjects affected / exposed	3 / 44 (6.82%)	1 / 19 (5.26%)	3 / 23 (13.04%)
occurrences (all)	3	1	3
Constipation			
subjects affected / exposed	10 / 44 (22.73%)	2 / 19 (10.53%)	6 / 23 (26.09%)
occurrences (all)	11	2	6
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Cholestasis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Hepatic function abnormal			
subjects affected / exposed	1 / 44 (2.27%)	0 / 19 (0.00%)	3 / 23 (13.04%)
occurrences (all)	1	0	3
Skin and subcutaneous tissue disorders			

Decubitus ulcer			
subjects affected / exposed	0 / 44 (0.00%)	0 / 19 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	3
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	5 / 44 (11.36%)	0 / 19 (0.00%)	1 / 23 (4.35%)
occurrences (all)	5	0	1
Oliguria			
subjects affected / exposed	5 / 44 (11.36%)	1 / 19 (5.26%)	3 / 23 (13.04%)
occurrences (all)	5	1	3
Dysuria			
subjects affected / exposed	0 / 44 (0.00%)	0 / 19 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Acute kidney injury			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 44 (6.82%)	1 / 19 (5.26%)	2 / 23 (8.70%)
occurrences (all)	3	1	2
Back pain			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Pain in extremity			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	2 / 23 (8.70%)
occurrences (all)	2	1	3
Plantar fasciitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Rhabdomyolysis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0

Infections and infestations			
Diverticulitis intestinal haemorrhagic			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Escherichia infection			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Pneumonia			
subjects affected / exposed	9 / 44 (20.45%)	3 / 19 (15.79%)	3 / 23 (13.04%)
occurrences (all)	9	3	3
Pneumonia aspiration			
subjects affected / exposed	2 / 44 (4.55%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	2	1	1
Tracheobronchitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Covid-19			
subjects affected / exposed	2 / 44 (4.55%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Hyperglycaemia			
subjects affected / exposed	1 / 44 (2.27%)	2 / 19 (10.53%)	1 / 23 (4.35%)
occurrences (all)	1	2	1
Hyperchloraemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 19 (5.26%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			

subjects affected / exposed	4 / 44 (9.09%)	0 / 19 (0.00%)	0 / 23 (0.00%)
occurrences (all)	4	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 44 (2.27%)	3 / 19 (15.79%)	7 / 23 (30.43%)
occurrences (all)	1	3	9
Hypokalaemia			
subjects affected / exposed	10 / 44 (22.73%)	2 / 19 (10.53%)	6 / 23 (26.09%)
occurrences (all)	11	2	6
Hyponatraemia			
subjects affected / exposed	6 / 44 (13.64%)	1 / 19 (5.26%)	6 / 23 (26.09%)
occurrences (all)	6	1	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2020	• The age range for study inclusion was increased from up to 80 years old to up to 85 years old. In addition, the Glasgow Coma Scale (GCS) score range for study inclusion was increased from up to 14 to up to 15 • Updated text to clarify definition of low blood glucose (BG) • Updated text to clarify if a participant is discharged from the hospital prior to Hour 96, sites should still obtain neuroimaging prior to the participant departing the hospital • Updated text to clarify that participants can get a NCCT scan if an MRI is not possible and that Hour 96 MRI scan should be performed within 18 hours of the Hour 96 time point • Pharmacokinetic (PK) objectives related to evaluation of BIIB093 was updated • Added text to clarify the mechanism of injury for study inclusion; exclusion criteria for NCCT or MRI; use of transient vasopressor, interventional radiology procedures for embolization, vitamin K antagonists • Suicidal ideation assessment was added to the schedule of activities at baseline and follow-up • Updated text to clarify blinding procedure, storage requirement of BIIB093, laboratory yests for safety assessments • Qualified neurosurgical interventions (NSx) including decompressive craniectomy (DC) and requirement for imaging studies were clarified • The images used to determine the primary endpoint and the timing of scans for contusion volume were clarified; timing for analysis requiring delayed intubation was clarified.
13 November 2022	• The study population was expanded to include participants indicated for surgery and those with survivable polytrauma facilitated by the removal of midline shift and injury severity score thresholds. The dosing time window was extended to 10 hours to allow for additional participants to be treated including inter-hospital transfers. An interim analysis was conducted by a separate unblinded team that facilitated an early start to Phase 3 planning while continuing the Phase 2 as a blinded study • Clarified that exposure data from the 5 mg/day dose was the result of simulations • Added text pertaining to scans in relation to IPH evacuation, DC, or CMO was added to the NCCT and MRI, optional NCCT scans • Updated assessment language regarding MRI/NCCT • Primary endpoint was amended to increase statistical power to detect a meaningful treatment effect while recognizing any reduction in contusion volume is desirable to detect • The GOS-E at Day 180 was removed as an additional endpoint and added as one of the secondary endpoints. GOS-E at Day 90 was removed as a secondary endpoint and added as one of the additional endpoints • Change in total contusion volume (hematoma plus perihematomal edema) from baseline to 24 hours was added as one of the secondary endpoints • The additional endpoint stating the proportion of participants requiring NSx, including craniotomy and DC, was removed • The new endpoint of proportion of participants requiring DC or IPH evacuation between 24 and 96 hours after trauma was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination of trial due to strategic considerations, not for efficacy or safety reasons.

Notes: