Clinical trial results:
Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 (Glibenclamide) for Severe Cerebral Edema Following Large Hemispheric Infarction

Summary

EudraCT number	2017-004854-41
Trial protocol	GB DE CZ DK BE PT ES HU FI LT IT HR
Global end of trial date	18 August 2023

Results information

Result version number	v2 (current)
This version publication date	03 February 2024
First version publication date	04 January 2024
Version creation reason	• Correction of full data set Endpoint title updated

Trial information

Trial identification

Sponsor protocol code	252LH301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02864953
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	18 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 August 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 improves functional outcomes at Day 90 as measured by the modified Rankin Scale (mRS) when compared with placebo in subjects with Large Hemispheric Infarction (LHI).

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	29 August 2018
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	United States: 228
Country: Number of subjects enrolled	Brazil: 46
Country: Number of subjects enrolled	China: 45
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Belgium: 4

Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Korea, Republic of: 4
Worldwide total number of subjects	535
EEA total number of subjects	114

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)	300
From 65 to 84 years	233
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at investigative sites in the United States, Brazil, China, Spain, Japan, Australia, Portugal, Germany, United Kingdom, Finland, Canada, Israel, France, Taiwan, Hungary, Czech Republic, Italy, Belgium, Lithuania, Russia and South Korea from 29 August 2018 to 18 August 2023.

Pre-assignment

Screening details:

A total of 535 participants were enrolled and randomised, out of which 518 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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants were administered with BIIB093 matching placebo as an intravenous (IV) bolus on Day 1 followed by a continuous IV infusion for over 72 hours.

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:

Administered as specified in the treatment arm.

Arm title	BIIB093

Arm description:

Participants were administered with BIIB093 as an IV bolus on Day 1 followed by continuous IV infusion for over 72 hours.

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:

Administered as specified in the treatment arm.

Number of subjects in period 1	Placebo	BIIB093
Started	268	267
Completed	215	213
Not completed	53	54
Consent withdrawn by subject	1	-
Physician decision	4	2
Death	3	13
Adverse event	22	19
Reason not specified	14	12
Withdrew Prior to Dosing	9	8

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants were administered with BIIB093 matching placebo as an intravenous (IV) bolus on Day 1 followed by a continuous IV infusion for over 72 hours.	
Reporting group title	BIIB093
Reporting group description:	
Participants were administered with BIIB093 as an IV bolus on Day 1 followed by continuous IV infusion for over 72 hours.	

Reporting group values	Placebo	BIIB093	Total
Number of subjects	268	267	535
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	61.6	60.5	
standard deviation	± 10.81	± 11.17	-
Gender categorical Units: Subjects			
Male	164	169	333
Female	104	98	202
Ethnicity Units: Subjects			
Missing	1	2	3
Hispanic or Latino	36	41	77
Not Hispanic or Latino	228	223	451
Not reported	3	1	4
Race Units: Subjects			
Missing	3	2	5
American Indian or Alaska Native	1	1	2
Asian	53	51	104
Black or African American	21	19	40
Native Hawaiian or Other Pacific Islander	2	0	2
White	173	177	350
Not reported due to confidentiality regulations	3	1	4
Other	12	16	28

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 on Day 1 followed by a continuous IV infusion for over 72 hours.	
Reporting group title	BIIB093
Reporting group description:	
Participants were administered with BIIB093 as an IV bolus on Day 1 followed by continuous IV infusion for over 72 hours.	

Primary: Part 1: Percentage of Participants with Improvement in Functional Outcome at Day 90 Assessed via the Modified Rankin Scale (mRS)

End point title	Part 1: Percentage of Participants with Improvement in Functional Outcome at Day 90 Assessed via the Modified Rankin Scale (mRS)
End point description:	
The mRS measures the degree of functional independence following stroke. In this study, the 7-category ordinal mRS scale was condensed to the following 5-categories: 0/1, 2, 3, 4, 5/6 where 0 and 1 reflect no disability and near-normal functioning while 5 and 6 represent severe disability and death, respectively. The modified intent to treat (mITT) population included participants aged 18 to 70 years (inclusive) at the time of randomisation, who had received any study drug, and who had at least 1 post-baseline mRS before or at the Day 90 visit. Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis.	
End point type	Primary
End point timeframe:	
Day 90	

End point values	Placebo	BIIB093		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	217		
Units: percentage of participants				
number (not applicable)				
Score: 0/1	1.4	3.2		
Score: 2	2.8	5.1		
Score: 3	12.6	12.0		
Score: 4	25.2	23.5		
Score: 5/6	57.9	56.2		

Statistical analyses

Statistical analysis title	Placebo Vs BIIB093
Comparison groups	Placebo v BIIB093

Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.415 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.71

Notes:

[1] - P-value was analyzed by ordinal logistic regression adjusting for covariates: region, and IRT stratification factors including rtPA usage (yes/no), thrombectomy usage (yes/no), use of ASPECTS for screening (yes/no), baseline NIHSS (<=20 vs. >20).

Secondary: Part 1: Time to All-Cause Death Through Day 90

End point title	Part 1: Time to All-Cause Death Through Day 90

End point description:

Time to all-cause death is defined as the time from randomization to the time of death.
The mITT population included participants aged 18 to 70 years (inclusive) at the time of randomisation, who received any study drug, and who had at least 1 post-baseline mRS before or at the Day 90 visit.
Here, 'subjects analysed' signifies the number of participants with data available for endpoint analysis.
9999 indicates that median and upper limit of inter quartile range were not reached due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Randomisation up to Day 90

End point values	Placebo	BIIB093		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	217		
Units: days				
median (inter-quartile range (Q1-Q3))	9999 (37 to 9999)	9999 (18 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Percentage of Participants Who Achieved mRS 0-4 at Day 90

End point title	Part 1: Percentage of Participants Who Achieved mRS 0-4 at Day 90

End point description:

The mRS measures the degree of functional independence following stroke. In this study, the 7-category ordinal mRS scale was condensed to the following 5-categories: 0/1, 2, 3, 4, 5/6 where 0 and 1 reflect no disability and near-normal functioning while 5 and 6 represent severe disability and death,

respectively.
The mITT population included participants aged 18 to 70 years (inclusive) at the time of randomisation, who received any study drug, and who had at least 1 post-baseline mRS before or at the Day 90 visit. 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		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	217		
Units: percentage of participants				
number (not applicable)	41.6	42.9		

Statistical analyses

Statistical analysis title	Placebo Vs BIIB093
Comparison groups	Placebo v BIIB093
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7413 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.6

Notes:

[2] - A logistic regression model was used to estimate an odds ratio (and 95% CI) of improvement on the mRS dichotomized as 0-4 vs. 5-6 at Day 90.

Secondary: Part 1: Midline Shift at 72 Hours as Assessed by Non-contrast Computed Tomography (NCCT) or Magnetic Resonance Imaging (MRI)

End point title	Part 1: Midline Shift at 72 Hours as Assessed by Non-contrast Computed Tomography (NCCT) or Magnetic Resonance Imaging (MRI)

End point description:

Midline shift is the perpendicular distance between the septum pellucidum and the line drawn between the anterior and posterior attachments of the falx to the inner table of the skull. The mITT population included participants aged 18 to 70 years (inclusive) at the time of randomization, who received any study drug, and who had at least 1 post-baseline mRS before or at the Day 90 visit. Here, 'subjects analysed' signifies number of participants with data available for endpoint analysis.

End point type	Secondary

End point timeframe:

At 72 hours

End point values	Placebo	BIIB093		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	155		
Units: millimeters (mm)				
arithmetic mean (standard deviation)	6.32 (± 4.760)	7.02 (± 4.565)		

Statistical analyses

Statistical analysis title	Placebo Vs BIIB093
Comparison groups	Placebo v BIIB093
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1242 [3]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	1.87

Notes:

[3] - Analysis of Variance (ANOVA) was used to compare the two study arms to assess the treatment effects on midline shift.

Secondary: Part 1: Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Part 1: Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. A 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.
The safety population included all participants who were enrolled and had received any portion of the infusion of study treatment (placebo or BIIB093). Here, 'subjects analysed' signifies number of participants with data available for endpoint analysis.

End point type	Secondary

End point timeframe:

From the signing of informed consent up to last follow-up visit (up to 4 years 11 months)

End point values	Placebo	BIIB093		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: percentage of participants				
number (not applicable)				
AEs	95.4	97.3		
SAEs	68.3	76.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of informed consent up to the last follow-up visit (up to 4 years 11 months)

Adverse event reporting additional description:

The safety population included all participants who were enrolled and had received any portion of the infusion of study treatment (placebo or BIIB093).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	BIIB093

Reporting group description:

Participants were administered with BIIB093 as an IV bolus followed by continuous IV infusion for over 72 hours.

Reporting group title	Placebo

Reporting group description:

Participants were administered with BIIB093 matching placebo as an IV bolus followed by a continuous IV infusion for over 72 hours.

Serious adverse events	BIIB093	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	199 / 259 (76.83%)	177 / 259 (68.34%)	
number of deaths (all causes)	104	97	
number of deaths resulting from adverse events	104	97	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cardiac myxoma			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Lung neoplasm malignant			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian clear cell carcinoma			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian epithelial cancer metastatic			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Renal cell carcinoma			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	5 / 259 (1.93%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 9	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Circulatory collapse			

subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Arteriosclerosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemodynamic instability			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Shock			
subjects affected / exposed	1 / 259 (0.39%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Hypotension			
subjects affected / exposed	0 / 259 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral artery occlusion			

subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reperfusion injury			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Malaise			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 259 (1.16%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Chest pain			
subjects affected / exposed	1 / 259 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac death			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			

subjects affected / exposed	3 / 259 (1.16%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	6 / 259 (2.32%)	6 / 259 (2.32%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 6	0 / 2	
Chronic respiratory failure			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Choking			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchospasm			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 259 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Obstructive airways disorder			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 259 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory arrest			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory acidosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 259 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Respiratory depression			

subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	8 / 259 (3.09%)	8 / 259 (3.09%)	
occurrences causally related to treatment / all	0 / 10	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 5	
Respiratory failure			
subjects affected / exposed	10 / 259 (3.86%)	11 / 259 (4.25%)	
occurrences causally related to treatment / all	0 / 11	0 / 11	
deaths causally related to treatment / all	0 / 7	0 / 9	
Respiratory distress			
subjects affected / exposed	2 / 259 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Delirium tremens			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 259 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression suicidal			
subjects affected / exposed	2 / 259 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neurological examination abnormal			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anticoagulation drug level below therapeutic			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Intentional overdose			

subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic ulcer haemorrhage			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain herniation			
subjects affected / exposed	19 / 259 (7.34%)	16 / 259 (6.18%)	
occurrences causally related to treatment / all	0 / 19	1 / 17	
deaths causally related to treatment / all	0 / 15	0 / 11	
Fall			
subjects affected / exposed	4 / 259 (1.54%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological procedural complication			
subjects affected / exposed	11 / 259 (4.25%)	12 / 259 (4.63%)	
occurrences causally related to treatment / all	0 / 11	0 / 13	
deaths causally related to treatment / all	0 / 1	0 / 2	
Post procedural haematoma			
subjects affected / exposed	2 / 259 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	2 / 259 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural haemorrhage			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 259 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Cardiac failure			
subjects affected / exposed	1 / 259 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Atrial fibrillation			
subjects affected / exposed	2 / 259 (0.77%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bradycardia			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	5 / 259 (1.93%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 4	0 / 4	

Acute myocardial infarction			
subjects affected / exposed	1 / 259 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Ventricular tachycardia			
subjects affected / exposed	0 / 259 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Ventricular fibrillation			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Tachycardia paroxysmal			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dilated cardiomyopathy			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	2 / 259 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Acute coronary syndrome			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac ventricular thrombosis			
subjects affected / exposed	2 / 259 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 259 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Nervous system disorders			
Cerebellar haemorrhage			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	10 / 259 (3.86%)	8 / 259 (3.09%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 8	0 / 7	
Brain compression			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	72 / 259 (27.80%)	79 / 259 (30.50%)	
occurrences causally related to treatment / all	0 / 83	1 / 85	
deaths causally related to treatment / all	0 / 35	0 / 48	
Brain stem haemorrhage			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral mass effect			
subjects affected / exposed	4 / 259 (1.54%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Lacunar stroke			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Embolic cerebral infarction			

subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 259 (0.77%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic cerebellar infarction			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhagic cerebral infarction			
subjects affected / exposed	1 / 259 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebral artery occlusion			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			

subjects affected / exposed	3 / 259 (1.16%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychogenic seizure			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post stroke epilepsy			
subjects affected / exposed	4 / 259 (1.54%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhagic transformation stroke			
subjects affected / exposed	14 / 259 (5.41%)	16 / 259 (6.18%)	
occurrences causally related to treatment / all	0 / 17	0 / 16	
deaths causally related to treatment / all	0 / 7	0 / 12	
Hydrocephalus			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intensive care unit acquired weakness			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	8 / 259 (3.09%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 5	0 / 2	
Lacunar infarction			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			

subjects affected / exposed	17 / 259 (6.56%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 17	0 / 5	
deaths causally related to treatment / all	0 / 14	0 / 5	
Malignant middle cerebral artery syndrome			
subjects affected / exposed	2 / 259 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Migraine			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	14 / 259 (5.41%)	6 / 259 (2.32%)	
occurrences causally related to treatment / all	0 / 15	0 / 6	
deaths causally related to treatment / all	0 / 12	0 / 5	
Status epilepticus			
subjects affected / exposed	1 / 259 (0.39%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	6 / 259 (2.32%)	10 / 259 (3.86%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 3	
Subdural hygroma			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 259 (0.77%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Blood loss anaemia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pelvic floor hernia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	2 / 259 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Constipation			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	2 / 259 (0.77%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 259 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	

Acute kidney injury			
subjects affected / exposed	7 / 259 (2.70%)	3 / 259 (1.16%)	
occurrences causally related to treatment / all	1 / 7	0 / 3	
deaths causally related to treatment / all	1 / 4	0 / 2	
Renal tubular necrosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus enteritis			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acinetobacter infection			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 pneumonia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Covid-19			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Clostridium difficile colitis			
subjects affected / exposed	3 / 259 (1.16%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterobacter pneumonia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cystitis			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	2 / 259 (0.77%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Enterococcal sepsis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia staphylococcal			
subjects affected / exposed	3 / 259 (1.16%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Pneumonia klebsiella			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia haemophilus			

subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	5 / 259 (1.93%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Gas gangrene			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	13 / 259 (5.02%)	18 / 259 (6.95%)	
occurrences causally related to treatment / all	0 / 17	0 / 21	
deaths causally related to treatment / all	0 / 9	0 / 8	
Neurosyphilis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella urinary tract infection			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematological infection			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	5 / 259 (1.93%)	5 / 259 (1.93%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 6	0 / 7	
Urinary tract infection			

subjects affected / exposed	6 / 259 (2.32%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tracheobronchitis			
subjects affected / exposed	3 / 259 (1.16%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 259 (0.00%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 259 (0.39%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	6 / 259 (2.32%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 4	
Sepsis			
subjects affected / exposed	6 / 259 (2.32%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 1	
Respiratory tract infection			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal abscess			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Proteus infection			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	4 / 259 (1.54%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			

subjects affected / exposed	0 / 259 (0.00%)	2 / 259 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 259 (0.00%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperkalaemia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoalbuminaemia			

subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoglycaemia			
subjects affected / exposed	15 / 259 (5.79%)	4 / 259 (1.54%)	
occurrences causally related to treatment / all	19 / 22	1 / 4	
deaths causally related to treatment / all	7 / 10	1 / 3	
Hyponatraemia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 259 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 259 (0.39%)	1 / 259 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	BIIB093	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	201 / 259 (77.61%)	199 / 259 (76.83%)	
Investigations			
Electrocardiogram qt prolonged			
subjects affected / exposed	6 / 259 (2.32%)	13 / 259 (5.02%)	
occurrences (all)	6	14	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	16 / 259 (6.18%)	9 / 259 (3.47%)	
occurrences (all)	25	11	
Hypotension			

subjects affected / exposed	14 / 259 (5.41%)	18 / 259 (6.95%)	
occurrences (all)	15	19	
Hypertension			
subjects affected / exposed	7 / 259 (2.70%)	13 / 259 (5.02%)	
occurrences (all)	9	14	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	13 / 259 (5.02%)	13 / 259 (5.02%)	
occurrences (all)	13	13	
Atrial fibrillation			
subjects affected / exposed	17 / 259 (6.56%)	22 / 259 (8.49%)	
occurrences (all)	20	27	
Nervous system disorders			
Haemorrhagic transformation stroke			
subjects affected / exposed	16 / 259 (6.18%)	24 / 259 (9.27%)	
occurrences (all)	18	28	
Headache			
subjects affected / exposed	22 / 259 (8.49%)	27 / 259 (10.42%)	
occurrences (all)	30	31	
Brain oedema			
subjects affected / exposed	28 / 259 (10.81%)	28 / 259 (10.81%)	
occurrences (all)	31	29	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	66 / 259 (25.48%)	57 / 259 (22.01%)	
occurrences (all)	90	119	
Pain			
subjects affected / exposed	14 / 259 (5.41%)	8 / 259 (3.09%)	
occurrences (all)	18	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	25 / 259 (9.65%)	28 / 259 (10.81%)	
occurrences (all)	33	38	
Leukocytosis			
subjects affected / exposed	16 / 259 (6.18%)	21 / 259 (8.11%)	
occurrences (all)	17	23	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 259 (5.02%)	24 / 259 (9.27%)	
occurrences (all)	16	29	
Dysphagia			
subjects affected / exposed	13 / 259 (5.02%)	6 / 259 (2.32%)	
occurrences (all)	14	6	
Constipation			
subjects affected / exposed	40 / 259 (15.44%)	54 / 259 (20.85%)	
occurrences (all)	45	64	
Vomiting			
subjects affected / exposed	22 / 259 (8.49%)	26 / 259 (10.04%)	
occurrences (all)	23	32	
Nausea			
subjects affected / exposed	13 / 259 (5.02%)	17 / 259 (6.56%)	
occurrences (all)	13	18	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	10 / 259 (3.86%)	20 / 259 (7.72%)	
occurrences (all)	10	23	
Acute kidney injury			
subjects affected / exposed	17 / 259 (6.56%)	11 / 259 (4.25%)	
occurrences (all)	19	11	
Infections and infestations			
Pneumonia aspiration			
subjects affected / exposed	15 / 259 (5.79%)	14 / 259 (5.41%)	
occurrences (all)	16	15	
Pneumonia			
subjects affected / exposed	32 / 259 (12.36%)	40 / 259 (15.44%)	
occurrences (all)	32	44	
Urinary tract infection			
subjects affected / exposed	29 / 259 (11.20%)	41 / 259 (15.83%)	
occurrences (all)	31	52	
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	26 / 259 (10.04%)	23 / 259 (8.88%)	
occurrences (all)	33	24	

Hyperglycaemia			
subjects affected / exposed	14 / 259 (5.41%)	15 / 259 (5.79%)	
occurrences (all)	18	41	
Hypocalcaemia			
subjects affected / exposed	13 / 259 (5.02%)	11 / 259 (4.25%)	
occurrences (all)	14	11	
Hypoglycaemia			
subjects affected / exposed	31 / 259 (11.97%)	8 / 259 (3.09%)	
occurrences (all)	54	18	
Hypokalaemia			
subjects affected / exposed	35 / 259 (13.51%)	32 / 259 (12.36%)	
occurrences (all)	44	36	
Hyponatraemia			
subjects affected / exposed	18 / 259 (6.95%)	18 / 259 (6.95%)	
occurrences (all)	20	21	
Hypophosphataemia			
subjects affected / exposed	14 / 259 (5.41%)	23 / 259 (8.88%)	
occurrences (all)	15	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2020	Increased the permitted percentage of subjects with endovascular thrombectomy performed prior to randomisation. The total daily dose was revised. The planned size of the primary efficacy population (≤70 years of age) was adjusted. Inclusion criterion 8 was revised to define time to randomization in relation to time of last known normal or symptom onset. Text was revised to remove laboratory tests that are not considered essential to laboratory safety assessments. Conditions under which study treatment must be permanently discontinued were revised to include management of study treatment in the presence of hypoglycemia. Withdrawal of subjects from the study was updated to specify that subjects who withdraw from the study may not be replaced. The Synopsis was revised to note the increase in the number of study sites. The text stating that BIIB093 is being studied for brain contusion as well as large hemispheric infarction was added. The Schedule of Activities was revised to include 'The Day 90 visit should be conducted in person whenever possible followed by telemedicine or phone in order of preference. All other visits after hospital discharge can be conducted by telephone/telemedicine or in person at the study subject's/representative's request'. Text regarding early termination was added; 'Early termination is defined as withdrawal from the study. Subjects who discontinue study treatment for any reason or who move to comfort care/palliative care should not be withdrawn from the study (see Section 10.1). Rather, they should either continue protocol-required tests and assessments or continue in the study with a limited study assessment schedule'. Text stating Pre-morbid mRS will be collected based on all available information including medical records, patient, family, and/or LAR reports was added as a footnote. Text was revised to allow more flexibility for PK and matrix metalloproteinase-9 (MMP-9) sampling around the time of the bolus infusion.
11 June 2021	Text regarding interim analysis was updated - An interim futility analysis may be performed based on the primary endpoint when approximately 30% of planned mITT participants complete Day 90

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 operational challenges and other strategic considerations, not for efficacy or safety reasons.

Notes: