



Clinical trial results:

Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous BII093 (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 | v1 |
| This version publication date | 04 January 2024 |
| First version publication date | 04 January 2024 |

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

| | |
|-----------------|---|
| End point title | Part 1: Reduction in 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 (\pm 4.760) | 7.02 (\pm 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 occurrences (all) | 14 / 259 (5.41%) 15 | 18 / 259 (6.95%) 19 | |
| Hypertension subjects affected / exposed occurrences (all) | 7 / 259 (2.70%) 9 | 13 / 259 (5.02%) 14 | |
| Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) | 13 / 259 (5.02%) 13 | 13 / 259 (5.02%) 13 | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 17 / 259 (6.56%) 20 | 22 / 259 (8.49%) 27 | |
| Nervous system disorders Haemorrhagic transformation stroke subjects affected / exposed occurrences (all) | 16 / 259 (6.18%) 18 | 24 / 259 (9.27%) 28 | |
| Headache subjects affected / exposed occurrences (all) | 22 / 259 (8.49%) 30 | 27 / 259 (10.42%) 31 | |
| Brain oedema subjects affected / exposed occurrences (all) | 28 / 259 (10.81%) 31 | 28 / 259 (10.81%) 29 | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 66 / 259 (25.48%) 90 | 57 / 259 (22.01%) 119 | |
| Pain subjects affected / exposed occurrences (all) | 14 / 259 (5.41%) 18 | 8 / 259 (3.09%) 10 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 25 / 259 (9.65%) 33 | 28 / 259 (10.81%) 38 | |
| Leukocytosis subjects affected / exposed occurrences (all) | 16 / 259 (6.18%) 17 | 21 / 259 (8.11%) 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 | <p>Increased the permitted percentage of subjects with endovascular thrombectomy performed prior to randomisation.</p> <p>The total daily dose was revised.</p> <p>The planned size of the primary efficacy population (≤ 70 years of age) was adjusted.</p> <p>Inclusion criterion 8 was revised to define time to randomization in relation to time of last known normal or symptom onset.</p> <p>Text was revised to remove laboratory tests that are not considered essential to laboratory safety assessments.</p> <p>Conditions under which study treatment must be permanently discontinued were revised to include management of study treatment in the presence of hypoglycemia.</p> <p>Withdrawal of subjects from the study was updated to specify that subjects who withdraw from the study may not be replaced.</p> <p>The Synopsis was revised to note the increase in the number of study sites.</p> <p>The text stating that BIIB093 is being studied for brain contusion as well as large hemispheric infarction was added.</p> <p>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'.</p> <p>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'.</p> <p>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.</p> <p>Text was revised to allow more flexibility for PK and matrix metalloproteinase-9 (MMP-9) sampling around the time of the bolus infusion.</p> |
| 11 June 2021 | <p>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</p> |

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: