



Clinical trial results:

A prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study to assess the efficacy and safety of clazosentan in preventing clinical deterioration due to delayed cerebral ischemia (DCI), in adult subjects with aneurysmal subarachnoid hemorrhage (aSAH)

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2018-000241-39 |
| Trial protocol | FI DE SE FR CZ BE DK HU AT PL ES IT |
| Global end of trial date | 18 November 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 30 November 2023 |
| First version publication date | 30 November 2023 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | ID-054-304 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03585270 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name | Idorsia Pharmaceuticals Ltd |
| Sponsor organisation address | Hegenheimermattweg 91, Allschwil, Switzerland, 4123 |
| Public contact | Idorsia Clinical Trial Information , Idorsia Pharmaceuticals Ltd, +41 58 844 19 77, idorsiaclinicaltrials@idorsia.com |
| Scientific contact | Idorsia Clinical Trial Information , Idorsia Pharmaceuticals Ltd, +41 58 844 19 77, idorsiaclinicaltrials@idorsia.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|------------------------------------------------------|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 27 January 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 November 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of clazosentan in preventing clinical deterioration due to DCI, in subjects with aSAH.

Protection of trial subjects:

Prior to the start of the study, each study site consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation. The protocol and any materials provided to the subject (such as a subject information sheet or description of the study used to obtain informed consent) were reviewed and approved by the appropriate IEC or IRB before the study was started. Sponsor personnel and the investigators were required to conduct the study in full compliance with ICH-GCP Guidelines, the principles of the Declaration of Helsinki, and with the laws and regulations in the country in which the study is conducted. The sponsor had the right to terminate the study at any time globally or locally. The investigators had the right to terminate the participation of their site in the study at any time. The investigator was responsible for protecting the subject's best interests. Study-specific criteria for discontinuation were described in the protocol. The investigators were responsible for maintaining the subjects' identities in strictest confidence. Written informed consent to participate in the study had to be obtained from the participant or proxy/legal representative at any time from hospital admission to prior to initiation of any study-mandated procedure. The informed consent was obtained prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study. It was made clear to each subject that he or she was completely free to refuse to enter the study, or to withdraw from the study at any time for any reason.

Background therapy:

The usual standard of care for the management of aSAH was allowed until the primary endpoint assessment at 14 days post-study drug initiation, except for those therapies listed in the "forbidden concomitant medication" section and must be documented in the medical charts. Nimodipine (oral or i.v.) could be administered for the usual duration if it was routine standard of care at the site.

"Statins" (e.g., simvastatin, pravastatin) could only be administered if the subject was receiving them chronically for the treatment of high cholesterol levels.

Vaccines (including those for COVID-19) could be administered at any time during the study.

For the purpose of this study, rescue therapy referred to the escalation of medical therapy beyond standard hemodynamic therapy, for the treatment of refractory vasospasm. The following therapies were considered rescue therapies:

- balloon angioplasty,
- intra-arterial, intrathecal/intra-cisternal/intra-ventricular administration of vasodilators or ozagrel.

The decision to administer the above rescue therapies was based on local standard of care and was allowed at any time during the study for refractory vasospasm.

Intravenous administration of vasodilators (e.g., nicardipine, milrinone) was allowed as rescue therapy only if preceded by intra-arterial administration of a vasodilator.

Study drug had to be temporarily interrupted prior to any rescue therapy and had to be resumed after the completion of the therapy.

Evidence for comparator: -

| | |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment | 03 February 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 16 |
| Country: Number of subjects enrolled | Spain: 48 |
| Country: Number of subjects enrolled | Sweden: 18 |
| Country: Number of subjects enrolled | Austria: 12 |
| Country: Number of subjects enrolled | Belgium: 32 |
| Country: Number of subjects enrolled | Czech Republic: 47 |
| Country: Number of subjects enrolled | Denmark: 5 |
| Country: Number of subjects enrolled | Finland: 25 |
| Country: Number of subjects enrolled | France: 33 |
| Country: Number of subjects enrolled | Germany: 42 |
| Country: Number of subjects enrolled | Hungary: 7 |
| Country: Number of subjects enrolled | United States: 59 |
| Country: Number of subjects enrolled | Canada: 20 |
| Country: Number of subjects enrolled | Israel: 13 |
| Country: Number of subjects enrolled | Italy: 29 |
| Worldwide total number of subjects | 406 |
| EEA total number of subjects | 314 |

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) | 346 |
| From 65 to 84 years | 60 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was done from 03 February 2019 to 18 November 2022.

Pre-assignment

Screening details:

406 participants are considered to be enrolled in the study. 3 of the 409 participants randomized did not receive treatment.

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, Monitor, Data analyst, Carer |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-------------|
| Arm title | Clazosentan |
|------------------|-------------|

Arm description:

All participants from the randomized analysis set who started clazosentan 15 mg per hour infusion for up to 14 days.

| | |
|----------------------------------------|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Clazosentan |
| Investigational medicinal product code | ACT-108475 |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects were administered a continuous infusion of clazosentan at a rate of 15 mg/hour.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo matching clazosentan was administered after randomization for a maximum of 14 days.

| | |
|----------------------------------------|---------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects were administered a continuous infusion of placebo matching clazosentan for up to 14 days.

| Number of subjects in period 1 | Clazosentan | Placebo |
|------------------------------------------|-------------|---------|
| Started | 202 | 204 |
| Completed | 167 | 190 |
| Not completed | 35 | 14 |
| Adverse event, serious fatal | 7 | 3 |
| Consent withdrawn by subject | 1 | 1 |
| Adverse event, non-fatal | 20 | 8 |
| Other reasons | 5 | 2 |
| Withdrawal by proxy/legal representative | 2 | - |

Baseline characteristics

Reporting groups

| | |
|----------------------------------------------------------------------------------------------------------------------|-------------|
| Reporting group title | Clazosentan |
| Reporting group description: | |
| All participants from the randomized analysis set who started clazosentan 15 mg per hour infusion for up to 14 days. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo matching clazosentan was administered after randomization for a maximum of 14 days. | |

| Reporting group values | Clazosentan | Placebo | Total |
|--------------------------------------------------------------------------------------------------------------------------|-------------|---------|-------|
| Number of subjects | 202 | 204 | 406 |
| Age categorical | | | |
| Age at hospital admission | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 171 | 175 | 346 |
| From 65-84 years | 31 | 29 | 60 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Age at hospital admission | | | |
| Units: years | | | |
| arithmetic mean | 53.0 | 53.7 | |
| standard deviation | ± 10.4 | ± 10.0 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 138 | 137 | 275 |
| Male | 64 | 67 | 131 |
| Race | | | |
| (United States NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 3 | 3 |
| Asian | 4 | 6 | 10 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 6 | 5 | 11 |
| White | 176 | 169 | 345 |
| Unknown or Not Reported | 16 | 21 | 37 |
| Ethnicity | | | |
| (NIH / OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 25 | 23 | 48 |
| Not Hispanic or Latino | 155 | 159 | 314 |
| Unknown or Not Reported | 22 | 22 | 44 |
| World Federation of Neurological Societies (WFNS) Grade | | | |
| The WFNS grade was assessed by the investigator at hospital admission. The WFNS grade ranges from I (best) to V (worst). | | | |
| Units: Subjects | | | |
| Grade I and II | 161 | 158 | 319 |

| | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|-----|
| Grade III to V | 41 | 46 | 87 |
| Aneurysmal subarachnoid hemorrhage diagnosed subgroups | | | |
| <p>High-risk prevention participants were diagnosed at an early stage of the disease continuum and were those who were at a high risk of developing cerebral vasospasm. These participants were characterized by the presence of a large quantity of subarachnoid blood on their hospital admission Computed Tomography (CT) scan (with a "thick and diffuse clot" defined as a thick confluent clot, more than 4 mm in thickness and involving more than 3 or more basal cisterns).</p> <p>The confirmed vasospasm participants did not have a "thick and diffuse clot" on their hospital admission CT scan.</p> | | | |
| Units: Subjects | | | |
| Confirmed vasospasm group | 6 | 5 | 11 |
| High risk of vasospasm group | 196 | 199 | 395 |
| Body Mass Index | | | |
| Units: kilogram(s)/square metre | | | |
| arithmetic mean | 26.8 | 26.8 | |
| standard deviation | ± 5.7 | ± 5.6 | - |
| Total Glasgow Coma Scale (GCS) Score | | | |
| <p>The GCS was performed at hospital admission. The GCS was used to measure the level of consciousness. Scores range from 3 (worst score) to 15 (best score).</p> | | | |
| Units: units on a scale | | | |
| arithmetic mean | 13.4 | 13.1 | |
| standard deviation | ± 3.0 | ± 3.3 | - |

End points

End points reporting groups

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Reporting group title | Clazosentan |
| Reporting group description: All participants from the randomized analysis set who started clazosentan 15 mg per hour infusion for up to 14 days. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo matching clazosentan was administered after randomization for a maximum of 14 days. | |
| Subject analysis set title | Clazosentan (safety set) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects treated with at least one infusion of clazosentan. | |
| Subject analysis set title | Placebo (safety set) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects treated with placebo infusion. | |

Primary: Occurrence of clinical deterioration due to delayed cerebral ischemia (DCI) from study drug initiation up to 14 days post-study drug initiation

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Occurrence of clinical deterioration due to delayed cerebral ischemia (DCI) from study drug initiation up to 14 days post-study drug initiation |
| End point description: Clinical deterioration due to delayed cerebral ischemia is defined as a worsening of at least 2 points compared to the reference score, on the modified Glasgow Coma Scale or the abbreviated National Institutes of Health Stroke Scale (aNIHSS), lasting for at least 2 hours, which cannot be entirely attributed to causes other than cerebral vasospasm. It is centrally adjudicated by the Clinical Event Committee (CEC) based on a written charter and review of clinical data, case narratives, angiograms and Computed Tomography scans. | |
| End point type | Primary |
| End point timeframe: Up to 14 days post-study drug initiation | |

| End point values | Clazosentan | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 202 | 204 | | |
| Units: subjects | 32 | 35 | | |

Statistical analyses

| | |
|----------------------------|-------------------------------------------------|
| Statistical analysis title | Relative Risk Reduction: Clazosentan vs Placebo |
| Comparison groups | Clazosentan v Placebo |

| | |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7338 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction |
| Point estimate | 0.072 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.426 |
| upper limit | 0.396 |

Secondary: Occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation

| | |
|-----------------|--------------------------------------------------------------------------------------------|
| End point title | Occurrence of clinically relevant cerebral infarction at Day 16 post-study drug initiation |
|-----------------|--------------------------------------------------------------------------------------------|

End point description:

A clinical relevant cerebral infarction was defined as: all-cause cerebral infarction greater than or equal to 5 cm³ or cerebral infarction less than 5 cm³ in participants with clinical deterioration due to delayed cerebral ischemia.

Cerebral infarction refers to new or worsened infarcts and was determined by a central radiology review comparing the total volume of infarcts on the computed tomography (CT) scan performed 16 days after study drug initiation with the total volume on the CT scan performed just prior to randomization.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Day 16 post study drug initiation

| End point values | Clazosentan | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 202 | 204 | | |
| Units: subjects | 15 | 23 | | |

Statistical analyses

| | |
|-----------------------------------------|-------------------------------------------------|
| Statistical analysis title | Relative Risk Reduction: Clazosentan vs Placebo |
| Comparison groups | Clazosentan v Placebo |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.177 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction |
| Point estimate | 0.341 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.213 |
| upper limit | 0.642 |

Secondary: Long-term Clinical Outcome Assessed by the Modified Rankin Scale (mRS) at Week 12 Post-aneurysmal Subarachnoid Hemorrhage (aSAH)

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Long-term Clinical Outcome Assessed by the Modified Rankin Scale (mRS) at Week 12 Post-aneurysmal Subarachnoid Hemorrhage (aSAH) |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|

End point description:

The modified Rankin Scale (mRS) was used to measure the degree of disability in participants who had a ruptured saccular aneurysm and were at a high risk of developing a delayed cerebral infarction (DCI). The mRS is scored by the physician. The mRS scores ranged from 0 (no symptoms) to 6 (dead). The mRS score was dichotomized into poor outcome (score greater and equal to 3) and good outcome (score less than 3).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Week 12 post-aneurysmal subarachnoid hemorrhage (aSAH)

| End point values | Clazosentan | Placebo | | |
|------------------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 202 | 204 | | |
| Units: Subjects | | | | |
| Subjects with a mRS score of equal and greater | 50 | 41 | | |
| Subjects with a mRS score of less than 3 | 152 | 163 | | |

Statistical analyses

| | |
|-----------------------------------------|-------------------------------------------------|
| Statistical analysis title | Relative Risk Reduction: Clazosentan vs placebo |
| Comparison groups | Clazosentan v Placebo |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1983 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction |
| Point estimate | -0.254 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.76 |
| upper limit | 0.107 |

Secondary: Long-term Clinical Outcome Assessed by the Glasgow Outcome Scale Extended (GOSE) at Week 12 Post-aSAH

| | |
|-----------------|-------------------------------------------------------------------------------------------------------|
| End point title | Long-term Clinical Outcome Assessed by the Glasgow Outcome Scale Extended (GOSE) at Week 12 Post-aSAH |
|-----------------|-------------------------------------------------------------------------------------------------------|

End point description:

The Glasgow Outcome Scale - Extended (GOSE) is a scale scored by the physician. The GOSE scores range from 1 (dead) to 8 (upper good recovery).

The long-term clinical outcome assessed by the GOSE was dichotomized into poor outcome (score ≤ 4) and good outcome (score > 4).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Week 12 post-aneurysmal subarachnoid hemorrhage (aSAH)

| End point values | Clazosentan | Placebo | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 202 | 204 | | |
| Units: Subjects | | | | |
| Subjects with a GOSE score ≤ 4 | 50 | 41 | | |
| Subjects with a GOSE score > 4 | 152 | 163 | | |

Statistical analyses

| | |
|-----------------------------------------|-------------------------------------------------|
| Statistical analysis title | Relative Risk Reduction: Clazosentan vs placebo |
| Comparison groups | Clazosentan v Placebo |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1983 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction |
| Point estimate | -0.254 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.76 |
| upper limit | 0.107 |

Other pre-specified: Occurrence of Clinical Deterioration Due to Delayed Cerebral Ischemia (DCI) From Study Drug Initiation up to 14 Days Post-study Drug Initiation (Safety Analysis Set)

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| End point title | Occurrence of Clinical Deterioration Due to Delayed Cerebral Ischemia (DCI) From Study Drug Initiation up to 14 Days Post- |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|

End point description:

Clinical deterioration due to delayed cerebral ischemia was defined as a worsening of at least 2 points compared to the reference score, on the modified Glasgow Coma Scale or the abbreviated National Institutes of Health Stroke Scale (aNIHSS), lasting for at least 2 hours, which could not be entirely attributed to causes other than cerebral vasospasm. It was centrally adjudicated by the Clinical Event Committee (CEC) based on a written charter and review of clinical data, case narratives, angiograms and computed tomography (CT) scans.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

| |
|------------------------------------------|
| Up to 14 days post-study drug initiation |
|------------------------------------------|

| End point values | Clazosentan (safety set) | Placebo (safety set) | | |
|-----------------------------|--------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 207 | 199 | | |
| Units: Subjects | 32 | 35 | | |

Statistical analyses

| Statistical analysis title | Relative Risk Reduction: Clazosentan vs. placebo |
|-----------------------------------------|--------------------------------------------------|
| Comparison groups | Clazosentan (safety set) v Placebo (safety set) |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5591 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction |
| Point estimate | 0.119 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.349 |
| upper limit | 0.425 |

Other pre-specified: Occurrence of Clinical Deterioration Due to Delayed Cerebral Ischemia (DCI) From Study Drug Initiation up to 14 Days Post-study Drug Initiation Including Rescue Therapy for Non-relevant Vasospasm

| | |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Occurrence of Clinical Deterioration Due to Delayed Cerebral Ischemia (DCI) From Study Drug Initiation up to 14 Days Post-study Drug Initiation Including Rescue Therapy for Non-relevant Vasospasm |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Clinical deterioration due to delayed cerebral ischemia was defined as a worsening of at least 2 points compared to the reference score, on the modified Glasgow Coma Scale or the abbreviated National Institutes of Health Stroke Scale (aNIHSS), lasting for at least 2 hours, which could not be entirely attributed to causes other than cerebral vasospasm. It was centrally adjudicated by the Clinical Event Committee (CEC) based on a written charter and review of

clinical data, case narratives, angiograms and Computed Tomograph (CT) scans.

| | |
|------------------------------------------|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| Up to 14 days post-study drug initiation | |

| End point values | Clazosentan | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 202 | 204 | | |
| Units: Subjects | 34 | 47 | | |

Statistical analyses

| | |
|-----------------------------------------|-------------------------------------------------|
| Statistical analysis title | Relative Risk Reduction: Clazosentan vs placebo |
| Comparison groups | Clazosentan v Placebo |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1179 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction |
| Point estimate | 0.267 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.085 |
| upper limit | 0.505 |

Other pre-specified: Occurrence of Clinical Deterioration Due to Delayed Cerebral Ischemia (DCI) From Study Drug Initiation up to 14 Days Post-study Drug Initiation Based on Neurological Scales and Death

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Occurrence of Clinical Deterioration Due to Delayed Cerebral Ischemia (DCI) From Study Drug Initiation up to 14 Days Post-study Drug Initiation Based on Neurological Scales and Death |
| End point description: | |
| Clinical deterioration due to delayed cerebral ischemia was defined as a worsening of at least 2 points compared to the reference score, on the modified Glasgow Coma Scale or the abbreviated National Institutes of Health Stroke Scale (aNIHSS), lasting for at least 2 hours, which could not be entirely attributed to causes other than cerebral vasospasm. It was centrally adjudicated by the Clinical Event Committee (CEC) based on a written charter and review of clinical data, case narratives, angiograms and Computed Tomograph (CT) scans. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Up to 14 days post-study drug initiation | |

| End point values | Clazosentan | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 202 | 204 | | |
| Units: Subjects | 28 | 33 | | |

Statistical analyses

| Statistical analysis title | Relative Risk Reduction: Clazosentan vs placebo |
|-----------------------------------------|-------------------------------------------------|
| Comparison groups | Clazosentan v Placebo |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5217 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative Risk Reduction |
| Point estimate | 0.139 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.365 |
| upper limit | 0.457 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were considered treatment-emergent, if the onset date was from the start of the first infusion on Day 1 to up to 24 hours after study treatment discontinuation. Study treatment was planned for up to 14 days.

Adverse event reporting additional description:

202 subjects were randomized and treated with clazosentan, an additional 5 subjects that had been randomized to placebo received at least one infusion of clazosentan.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Clazosentan 15 mg/h |
|-----------------------|---------------------|

Reporting group description:

Subjects that received at least one infusion of clazosentan 15 mg/hour.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| Serious adverse events | Clazosentan 15 mg/h | Placebo | |
|------------------------------------------------------|---------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 33 / 207 (15.94%) | 26 / 199 (13.07%) | |
| number of deaths (all causes) | 7 | 3 | |
| number of deaths resulting from adverse events | 5 | 1 | |
| Vascular disorders | | | |
| Distributive shock | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Aneurysm repair | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Brain death | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 207 (0.97%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 2 / 207 (0.97%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 207 (0.97%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Agitation | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Incision site discharge | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural complication | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Torsade de pointes | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 3 / 207 (1.45%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain oedema | | | |
| subjects affected / exposed | 4 / 207 (1.93%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 4 / 207 (1.93%) | 2 / 199 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebral microinfarction | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral vasoconstriction | | | |

| | | | |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed | 13 / 207 (6.28%) | 12 / 199 (6.03%) | |
| occurrences causally related to treatment / all | 1 / 15 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delayed ischaemic neurological deficit | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 3 / 207 (1.45%) | 3 / 199 (1.51%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 1 / 199 (0.50%) | |
| 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 | 2 / 207 (0.97%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Posthaemorrhagic hydrocephalus | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ruptured cerebral aneurysm | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 2 / 199 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (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 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Eye disorders | | | |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal compartment syndrome | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peptic ulcer | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatobiliary disorders | | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Meningitis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningoencephalitis herpetic | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonal bacteraemia | | | |
| subjects affected / exposed | 1 / 207 (0.48%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonas aeruginosa meningitis | | | |
| subjects affected / exposed | 0 / 207 (0.00%) | 1 / 199 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 3 / 207 (1.45%) | 0 / 199 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Clazosentan 15 mg/h | Placebo | |
|-------------------------------------------------------|---------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 156 / 207 (75.36%) | 140 / 199 (70.35%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 15 / 207 (7.25%) | 14 / 199 (7.04%) | |
| occurrences (all) | 16 | 14 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 13 / 207 (6.28%) | 9 / 199 (4.52%) | |
| occurrences (all) | 13 | 9 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 24 / 207 (11.59%) | 20 / 199 (10.05%) | |
| occurrences (all) | 24 | 20 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 10 / 207 (4.83%) | 26 / 199 (13.07%) | |
| occurrences (all) | 10 | 28 | |
| Hypotension | | | |
| subjects affected / exposed | 18 / 207 (8.70%) | 7 / 199 (3.52%) | |
| occurrences (all) | 18 | 9 | |
| Nervous system disorders | | | |
| Cerebral vasoconstriction | | | |
| subjects affected / exposed | 22 / 207 (10.63%) | 39 / 199 (19.60%) | |
| occurrences (all) | 27 | 56 | |
| Headache | | | |
| subjects affected / exposed | 31 / 207 (14.98%) | 23 / 199 (11.56%) | |
| occurrences (all) | 42 | 24 | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 13 / 207 (6.28%) | 5 / 199 (2.51%) | |
| occurrences (all) | 13 | 5 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 12 / 207 (5.80%) | 8 / 199 (4.02%) | |
| occurrences (all) | 14 | 8 | |
| General disorders and administration site conditions | | | |

| | | | |
|-------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| Pyrexia subjects affected / exposed occurrences (all) | 42 / 207 (20.29%) 44 | 35 / 199 (17.59%) 38 | |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 32 / 207 (15.46%) 37 | 28 / 199 (14.07%) 34 | |
| Nausea subjects affected / exposed occurrences (all) | 17 / 207 (8.21%) 17 | 6 / 199 (3.02%) 6 | |
| Vomiting subjects affected / exposed occurrences (all) | 17 / 207 (8.21%) 19 | 6 / 199 (3.02%) 6 | |
| Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences (all) | 15 / 207 (7.25%) 15 | 3 / 199 (1.51%) 3 | |
| Pulmonary oedema subjects affected / exposed occurrences (all) | 12 / 207 (5.80%) 12 | 2 / 199 (1.01%) 2 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 14 / 207 (6.76%) 14 | 11 / 199 (5.53%) 11 | |
| Renal and urinary disorders Polyuria subjects affected / exposed occurrences (all) | 7 / 207 (3.38%) 8 | 10 / 199 (5.03%) 10 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 6 / 207 (2.90%) 6 | 10 / 199 (5.03%) 10 | |
| Infections and infestations Pneumonia subjects affected / exposed occurrences (all) | 13 / 207 (6.28%) 13 | 6 / 199 (3.02%) 7 | |
| Urinary tract infection | | | |

| | | | |
|--------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 25 / 207 (12.08%) 25 | 24 / 199 (12.06%) 24 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 25 / 207 (12.08%) | 31 / 199 (15.58%) | |
| occurrences (all) | 28 | 37 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 33 / 207 (15.94%) | 29 / 199 (14.57%) | |
| occurrences (all) | 34 | 31 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12 February 2019 | <p>Protocol version 3 - Substantial amendment, dated 4 December 2018, to align the protocol with the IB Version 14 which had been amended to address requests received from the US FDA:</p> <ul style="list-style-type: none">• Restrictions were made concerning the contraception and breastfeeding requirements by extending them from 24 hours to 30 days post study treatment discontinuation.• Clarification was provided on certain study procedures and entry criteria, new/revised exploratory endpoints were added, and other minor modifications were done.• The statistical methods section was aligned with the most recent version of the statistical analysis plan. |
| 07 February 2020 | <p>Protocol version 4 - Substantial amendment, dated 07 January 2020, to add a Quality of Life assessment at 24 weeks (6 months) post-aSAH. The main changes are summarized below:</p> <ul style="list-style-type: none">• The EQ-5D questionnaire was added at Week 24 post-aSAH.• The EOS visit at the individual subject level was rescheduled to Week 24 post aSAH and the previous EOS visit was renamed 'Week 12 visit'.• SAE reporting was extended from up to 3 months to up to 6 months.• Clarification on supportive data collection for the primary endpoint was provided.• The rules for rescue therapy usage were clarified. |
| 14 August 2020 | <p>Protocol version 5 - Substantial amendment, dated 2 July 2020, to describe the follow-up and collection of data until Day 14 post-study treatment initiation for subjects who were discharged from the study site prior to Day 14. The main changes are summarized below:</p> <ul style="list-style-type: none">• A follow-up visit/phone call was introduced for subjects who were discharged from the study site prior to Day 14 post-study treatment initiation. The data to be collected and recorded during this follow-up were described.• It was explained how subjects who were discharged prior to Day 14 could meet the primary efficacy endpoint based on data collected between discharge and Day 14.• A separate dedicated section was added to describe the observation period for the primary endpoint.• Information concerning image archiving at the study sites was added. |
| 27 May 2021 | <p>Protocol version 6 - Substantial amendment, dated 29 April 2021, to discontinue recruitment into the early treatment group following a recommendation received from the study IDMC on 2 April 2021.</p> <p>The decision to discontinue recruitment into the early treatment group was not based on a planned interim efficacy analysis, nor on urgent safety observations but a low rate of recruitment into this cohort since the outset of the study, making the contribution of these subjects to the overall study futile.</p> |

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|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15 March 2022 | <p>Protocol version 7 - Substantial amendment, dated 18 February 2022, to modify the definition of the main secondary efficacy endpoint and the hierarchical statistical testing strategy related to the other secondary endpoints. The main changes are summarized below:</p> <ul style="list-style-type: none"> • The main secondary endpoint definition was updated: in addition to the already existing all-cause infarcts ≥ 5 cm³ at Day 16 post-study treatment initiation, clinically relevant infarcts < 5 cm³ were added. The latter were defined as those new or worsened infarcts < 5 cm³ that occurred in subjects with CEC-adjudicated clinical deterioration due to DCI. • The initial definition of the main secondary endpoint, i.e., all cause new or worsened infarcts ≥ 5 cm³ at Day 16 post-study treatment initiation was included as an exploratory endpoint. • In addition, the modified Rankin Scale was formally included in the statistical hierarchical testing strategy, prior to the GOSE. |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 20 March 2020 | Recruitment into the study was temporarily on hold due to the pandemic. The IRT system was inactive during the temporary recruitment hold. | 05 June 2020 |

Notes:

Limitations and caveats

None reported