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			
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). The confirmed vasospasm participants did not have a "thick and diffuse clot" on their hospital admission CT scan.			
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			
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).			
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

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 infraction greater than or equal to 5 cm^3 or cerebral infarction less than 5 cm^3 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-

	study Drug Initiation (Safety Analysis Set)

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

subjects affected / exposed	25 / 207 (12.08%)	24 / 199 (12.06%)	
occurrences (all)	25	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	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: • 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	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: • 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	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: • 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	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. 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.

15 March 2022	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: • 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