Clinical trial results:
A prospective, multi-center, open-label, single-arm, Phase 2 study to assess the efficacy and safety of clazosentan in reversing angiographically-confirmed cerebral vasospasm in adult subjects with aneurysmal subarachnoid hemorrhage (aSAH) treated by surgical clipping or endovascular coiling.

Summary

EudraCT number	2015-002721-18
Trial protocol	FI
Global end of trial date	15 May 2017

Results information

Result version number	v2 (current)
This version publication date	07 November 2019
First version publication date	23 June 2018
Version creation reason	• Correction of full data set Change of Sponsor

Trial information

Trial identification

Sponsor protocol code	AC-054-203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02560532
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Idorsia Pharmaceuticals Ltd
Sponsor organisation address	Hegenheimermattweg 91, Allschwil, Switzerland, 4123
Public contact	clinical trial disclosure desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com
Scientific contact	clinical trial disclosure desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@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	14 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether clazosentan has an early effect in reversing angiographically-confirmed cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage treated by endovascular coiling or surgical clipping.

The study used a Simon 2-stage design. Stage 1 analysis was planned to be performed on the first 10 evaluable subjects, while stage 2 analysis was planned to be conducted, assuming positive stage 1 analysis, on the first 19 evaluable subjects.
Criterion to continue to stage 2 (positive stage 1 analysis) is met if > 2 subjects with successful reversal were observed.

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 sponsor and the investigators ensured that the study was conducted in full compliance with International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) Guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the countries in which the research was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Switzerland: 4
Worldwide total number of subjects	14
EEA total number of subjects	10

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)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 11 sites in 3 countries from 21 March 2016 to 2 May 2017.

Pre-assignment

Screening details:

The study included a screening period of variable duration, starting any time after the aneurysm securing procedure and lasting up to a maximum of 14 days from the occurrence of the aneurysm to enrollment into the study.

At the time of study termination, 33 subjects had been screened and 14 subjects enrolled.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Clazosentan 15 mg/h

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Clazosentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Clazosentan was supplied as a concentrated solution for i.v. administration after dilution. The diluted study drug solution was administered as a continuous i.v. infusion at the dose of 15 mg/h for up to a cumulative maximum of 10 days.

Number of subjects in period 1	Clazosentan 15 mg/h
Started	14
Completed	14

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
Adults (18-64 years)	14	14	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	48.9		
standard deviation	± 8.58	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	1	1	
Race Units: Subjects			
Black or African American	1	1	
American Indian or Alaska	0	0	
Native	0	0	
Native Hawaiian or Other	0	0	
Pacific Islander	0	0	
Asian	1	1	
White	11	11	
Other	1	1	
World Federation of Neurological Societies grade Units: Subjects			
Grade I	7	7	
Grade II	1	1	
Grade III	0	0	
Grade IV	6	6	
Location of aneurysm Units: Subjects			
Supraclinoid internal carotid artery segments	3	3	
Middle cerebral artery segments	3	3	
Anterior cerebral artery segments	0	0	
Anterior communicating artery	4	4	
Posterior communicating artery	2	2	
Distal vertebral artery	0	0	
Basilar artery	0	0	
Posterior cerebral artery	0	0	

Other: pica	1	1	
Other: posterior inferior cerebellar artery	1	1	
Securing procedures Units: Subjects			
Clip	1	1	
Coil	13	13	
Clot Size Units: Subjects			
No visible clot	0	0	
Local thin	0	0	
Local thick	2	2	
Diffuse thin	1	1	
Diffuse thick	11	11	
Mechanical ventilation on the day of enrollment Units: Subjects			
Yes	3	3	
No	11	11	
Time elapsed between aneurysm rupture and start of treatment Units: Days			
arithmetic mean	7.6		
standard deviation	± 2.20	-	

End points

End points reporting groups

Reporting group title	Clazosentan 15 mg/h
Reporting group description: -	
Subject analysis set title	Evaluable set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Used for the main analysis of the primary and secondary endpoints and included subjects with:
Absence of violation of exclusion criteria related to forbidden medications and procedures.
Presence of a DSA evaluable for global cerebral vasospasm at baseline and at 3h / 24 h post-study drug initiation.

Primary: Successful reversal of global cerebral vasospasm (GV) 3 h post study drug initiation

End point title	Successful reversal of global cerebral vasospasm (GV) 3 h post study drug initiation[1]

End point description:

Successful reversal was defined as an improvement in at least one level of severity on the global vasospasm assessment (i.e., from severe to moderate, mild, or none, or from moderate to mild or none) evaluated on DSA. The presence/absence of vasospasm (vsp) was determined at the level of the following 15 proximal (vertebro basilar, left/right intradural ICA, left/right A1, left/right M1, left/right P1) and distal (left/right A2, left/right P2, left/right M2) brain vessels.
The severity of the vsp in each vessel segment was indicated as follows:
None: no vsp
Mild: up to 1/3 vessel narrowing
Moderate: more than 1/3 and up to 2/3 vessel narrowing
Severe: more than 2/3 vessel narrowing
The severity of global vsp was indicated as follows:
No significant vsp: ≤2 segments with mild vsp
Mild: >2 segments with mild and/or 1 segment with moderate vsp
Moderate: ≥2 segments with moderate and/or 1 segment with severe vsp
Severe: ≥2 segments with severe vsp

End point type	Primary

End point timeframe:

3 hours post study-drug initiation

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not applicable.

End point values	Evaluable set			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Subjects				
Subjects with successful reversal of GV	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Successful reversal of global cerebral vasospasm 24 hours (+/− 6 h) post-study drug initiation

End point title	Successful reversal of global cerebral vasospasm 24 hours (+/– 6 h) post-study drug initiation

End point description:

Successful reversal of global cerebral vasospasm was defined as described for the primary endpoint when a baseline DSA and a DSA at 24 h were both available

End point type	Secondary

End point timeframe:

24 hours post-study drug initiation

End point values	Evaluable set			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Subjects	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum change in angiographic cerebral circulation time from baseline to 3 hours

End point title	Maximum change in angiographic cerebral circulation time from baseline to 3 hours

End point description:

The maximum change in CCT from baseline to 3 hours is the largest of the differences between CCTs at baseline and CCTs at 3 hours, and the maximum change in CCT from baseline to 24 hours is the largest of the differences between CCTs at baseline and CCTs at 24 hours. This endpoint has been chosen to take into account changes in diameter of small cerebral vessels, not measurable on angiography

End point type	Secondary

End point timeframe:

From baseline to 3 hours

End point values	Evaluable set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Seconds				
median (full range (min-max))	-0.7 (-3.0 to 5.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum change in angiographic cerebral circulation time from baseline

to 24 hours

End point title	Maximum change in angiographic cerebral circulation time from baseline to 24 hours

End point description:

The maximum change in CCT from baseline to 3 hours is the largest of the differences between CCTs at baseline and CCTs at 3 hours, and the maximum change in CCT from baseline to 24 hours is the largest of the differences between CCTs at baseline and CCTs at 24 hours. This endpoint has been chosen to take into account changes in diameter of small cerebral vessels, not measurable on angiography

End point type	Secondary

End point timeframe:

From baseline to 24 hours

End point values	Evaluable set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Seconds				
median (full range (min-max))	-1.6 (-4.3 to 4.7)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Distribution of responding segments (i.e., score ≥ 2) by location at 3 h and 24 h

End point title	Distribution of responding segments (i.e., score ≥ 2) by location at 3 h and 24 h

End point description:

This endpoint was assessed post-hoc with the objective to better characterize the pharmacodynamic effect of clazosentan on the entire cerebral vasculature, including smaller distal vessel segments and the cerebellar arteries. This evaluation considered a larger number of vessel segments (29) than the primary endpoint evaluation (15 segments).

Segments were defined as proximal (ICA, A1, M1, vertebral artery, basilar artery, P1) or distal (A2, A3/A4, M2, M3/M4, P2, P3/P4, anterior inferior cerebellar artery, posterior inferior cerebellar artery, superior cerebellar artery). Each evaluable segment with significant vasospasm on the baseline angiogram was graded at 3 h and 24 h post initiation of clazosentan with a 7-level scoring system ranging from −3 for severe worsening to +3 for improvement back to admission state. A segment with a score ≥ 2 (corresponding to at least a significant improvement) was considered as responding.

End point type	Post-hoc

End point timeframe:

3 and 24 hours post study-drug initiation

End point values	Clazosentan 15 mg/h			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Number of evaluated segments				
Number of evaluated segments at 3 hours	176			
Number of evaluated segments at 24 hours	124			

Attachments (see zip file)	Number of evaluated segments.JPG

Statistical analyses

No statistical analyses for this end point

Post-hoc: Distribution of responding subjects (≥ 50% of segments with score ≥ 2) by location and time point

End point title	Distribution of responding subjects (≥ 50% of segments with score ≥ 2) by location and time point

End point description:

This endpoint was assessed post-hoc with the objective to better characterize the pharmacodynamic effect of clazosentan on the entire cerebral vasculature, including smaller distal vessel segments and the cerebellar arteries. This evaluation considered a larger number of vessel segments (29) than the primary endpoint evaluation (15 segments).

Segments were defined as proximal (ICA, A1, M1, vertebral artery, basilar artery, P1) or distal (A2, A3/A4, M2, M3/M4, P2, P3/P4, anterior inferior cerebellar artery, posterior inferior cerebellar artery, superior cerebellar artery). Each evaluable segment with significant vasospasm on the baseline angiogram was graded at 3 h and 24 h post initiation of clazosentan with a 7-level scoring system ranging from −3 for severe worsening to +3 for improvement back to admission state. A segment with a score ≥ 2 (corresponding to at least a significant improvement) was considered as responding.

End point type	Post-hoc

End point timeframe:

3 and 24 hours post-study drug initiation

End point values	Clazosentan 15 mg/h			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Number of evaluated subjects				
Number of subjects evaluated at 3 hours	14			
Number of subjects evaluated at 24 hours	9			

Attachments (see zip file)	Number of evaluated subjects.JPG

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Enter description here	
Adverse event reporting additional description:	
Enter description here	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Clazosentan 15mg/h
Reporting group description:	
Clazosentan	

Serious adverse events	Clazosentan 15mg/h		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Stress cardiomyopathy			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral vasoconstriction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Monoplegia			

subjects affected / exposed	2 / 14 (14.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Clazosentan 15mg/h		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Product issues			

Device occlusion			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Blood phosphorus decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood magnesium decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood potassium increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Ultrasound Doppler abnormal			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cell marker increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Vasoplegia syndrome			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Cardiac disorders			
Coronary artery occlusion			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nervous system disorders			
Cerebral vasoconstriction			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Cognitive disorder			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cerebral infarction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Motor dysfunction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hemianopia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eye disorders			
Mydriasis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Constipation			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Rash macular			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Lung infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Cerebral salt-wasting syndrome			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Dyslipidaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2016	Summary of most relevant changes: Modified entry criteria: - The CT scan at 2448 h post aneurysm-securing procedure was removed since any procedure-related injury would have been detected on the CT scan performed just prior to study enrollment. - The definition of severe hypoxemia was modified from PaO2/FiO2 < 300 to PaO2/FiO2 < 250, which was a more realistic definition of severe hypoxemia. - Upon sponsor approval at site level, a CTA could replace a missing or incomplete DSA, at hospital admission. definition of CCT secondary endpoint and how it was to be derived were made: CCT secondary endpoint definition: - The endpoint was modified from change in angiographic CCT to maximum change in angiographic CCT. The recommendation to perform the TCD at 3 h post study drug initiation was waived. Also, it was acceptable to perform the hourly TCD assessments only in the vessel that showed the highest mean flow velocity at baseline

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 May 2017	The study was ended prematurely after the planned stage 1 analysis revealed successful reversal of global cerebral vasospasm, based on the primary endpoint definition, in 2 out of the first 10 evaluable subjects. The protocol-specified statistical criterion to prematurely stop the study due to insufficient efficacy was met. However, the primary endpoint definition of successful reversal only considered the larger cerebral artery segments using a semi-quantitative evaluation. A second review of the angiograms was therefore performed, by two external experts, taking into account the smaller more distal artery segments and the cerebellar arteries, using a quantitative evaluation scale. The post-hoc analysis showed a clearly visible pharmacodynamic effect at 3 h, that was even more pronounced at 24 h, in a significant proportion of segments and subjects, in both large proximal and small distal vessels. This effect was also observed in cases that were judged to be unsuccessful reversals according to the pre-defined primary endpoint definition.	-

Notes:

Limitations and caveats

None reported