



## 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          | v1           |
| This version publication date  | 23 June 2018 |
| First version publication date | 23 June 2018 |

### 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    | Actelion Pharmaceuticals Ltd                                                                           |
| Sponsor organisation address | Gewerbestrasse 16, Allschwil, Switzerland, 4123                                                        |
| Public contact               | clinical trial disclosure desk, Idorsia Pharmaceuticals Ltd,<br>clinical-trials-disclosure@idorsia.com |
| Scientific contact           | clinical trial disclosure desk, Idorsia Pharmaceuticals Ltd,<br>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.

|                                       |                     |
|---------------------------------------|---------------------|
| <b>Number of subjects in period 1</b> | 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 Native                 | 0             | 0     |  |
| Native Hawaiian or Other Pacific Islander        | 0             | 0     |  |
| Asian                                            | 0             | 0     |  |
| White                                            | 1             | 1     |  |
| Other                                            | 11            | 11    |  |
| 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<br>Units: Subjects                                      |        |    |  |
| Clip                                                                        | 1      | 1  |  |
| Coil                                                                        | 13     | 13 |  |
| Clot Size<br>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<br>Units: Subjects          |        |    |  |
| Yes                                                                         | 3      | 3  |  |
| No                                                                          | 11     | 11 |  |
| Time elapsed between aneurysm rupture and start of treatment<br>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 <sup>[1]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------|

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: Following the planned stage 1 analysis the statistical criterion to proceed further to stage 2 was not met, leading to premature study discontinuation.

An exploratory analysis conducted on all evaluable subjects at end of study (n=11) has revealed that 3 subjects achieved a successful reversal of global cerebral vasospasm.

|                                         |                      |  |  |  |
|-----------------------------------------|----------------------|--|--|--|
| <b>End point values</b>                 | 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

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

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|                 |                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------|
| 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

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|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | Evaluable set        |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 7                    |  |  |  |
| Units: Subjects             | 2                    |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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

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|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| 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

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|                               |                      |  |  |  |
|-------------------------------|----------------------|--|--|--|
| <b>End point values</b>       | 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)   |  |  |  |

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**Statistical analyses**

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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

|                               |                      |  |  |  |
|-------------------------------|----------------------|--|--|--|
| <b>End point values</b>       | 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 $\geq 2$ ) by location at 3 h and 24 h

|                 |                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------|
| End point title | Distribution of responding segments (i.e., score $\geq 2$ ) 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  $\geq 2$  (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

|                                          |                     |  |  |  |
|------------------------------------------|---------------------|--|--|--|
| <b>End point values</b>                  | 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                 |  |  |  |

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Attachments (see zip file)</b> | Number of evaluated segments.JPG |
|-----------------------------------|----------------------------------|

### Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Distribution of responding subjects ( $\geq 50\%$ of segments with score $\geq 2$ ) 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  $\geq 2$  (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

|                                          |                     |  |  |  |
|------------------------------------------|---------------------|--|--|--|
| <b>End point values</b>                  | 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                   |  |  |  |

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Attachments (see zip file)</b> | Number of evaluated subjects.JPG |
|-----------------------------------|----------------------------------|

## Statistical analyses

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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 infarction                               |                    |  |  |
| subjects affected / exposed                       | 1 / 14 (7.14%)     |  |  |
| occurrences causally related to treatment / all   | 0 / 1              |  |  |
| deaths causally related to treatment / all        | 0 / 0              |  |  |
| 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              |  |  |
| 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 %

|                                                       |                    |  |  |
|-------------------------------------------------------|--------------------|--|--|
| <b>Non-serious adverse events</b>                     | Clazosentan 15mg/h |  |  |
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 12 / 14 (85.71%)   |  |  |
| Vascular disorders                                    |                    |  |  |
| Hypertension                                          |                    |  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)     |  |  |
| occurrences (all)                                     | 1                  |  |  |
| Deep vein thrombosis                                  |                    |  |  |
| 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<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 14 (7.14%)<br>1  |  |  |
| Investigations                                                                           |                      |  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 2 / 14 (14.29%)<br>2 |  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 14 (21.43%)<br>3 |  |  |
| Blood magnesium decreased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 14 (7.14%)<br>1  |  |  |
| Blood phosphorus decreased<br>subjects affected / exposed<br>occurrences (all)           | 1 / 14 (7.14%)<br>1  |  |  |
| Blood potassium increased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 14 (7.14%)<br>1  |  |  |
| Cell marker increased<br>subjects affected / exposed<br>occurrences (all)                | 1 / 14 (7.14%)<br>1  |  |  |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1  |  |  |
| Ultrasound Doppler abnormal<br>subjects affected / exposed<br>occurrences (all)          | 1 / 14 (7.14%)<br>1  |  |  |
| Injury, poisoning and procedural complications                                           |                      |  |  |
| Vasoplegia syndrome<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 14 (7.14%)<br>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 infarction                  |                 |  |  |
| subjects affected / exposed          | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Cerebral vasoconstriction            |                 |  |  |
| subjects affected / exposed          | 2 / 14 (14.29%) |  |  |
| occurrences (all)                    | 2               |  |  |
| Cognitive disorder                   |                 |  |  |
| subjects affected / exposed          | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Hemianopia                           |                 |  |  |
| 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               |  |  |
| 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               |  |  |
| Lung infection                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 14 (7.14%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Pneumonia                                       |                 |  |  |
| 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               |  |  |
| Dyslipidaemia               |                 |  |  |
| subjects affected / exposed | 1 / 14 (7.14%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hypokalaemia                |                 |  |  |
| subjects affected / exposed | 1 / 14 (7.14%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hyperglycaemia              |                 |  |  |
| subjects affected / exposed | 2 / 14 (14.29%) |  |  |
| occurrences (all)           | 2               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 June 2016 | <p>Summary of most relevant changes:</p> <p>Modified entry criteria:</p> <ul style="list-style-type: none"><li>- 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.</li><li>- The definition of severe hypoxemia was modified from <math>\text{PaO}_2/\text{FiO}_2 &lt; 300</math> to <math>\text{PaO}_2/\text{FiO}_2 &lt; 250</math>, which was a more realistic definition of severe hypoxemia.</li><li>- Upon sponsor approval at site level, a CTA could replace a missing or incomplete DSA, at hospital admission.</li></ul> <p>definition of CCT secondary endpoint and how it was to be derived were made:</p> <p>CCT secondary endpoint definition:</p> <ul style="list-style-type: none"><li>- The endpoint was modified from change in angiographic CCT to maximum change in angiographic CCT.</li></ul> <p>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</p> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date        | Interruption                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Restart date |
|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 15 May 2017 | <p>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.</p> <p>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.</p> | -            |

Notes:

### Limitations and caveats

None reported