



## Clinical trial results:

### Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study Comparing EG-1962 to Standard

### of Care Oral Nimodipine in Adults with Aneurysmal Subarachnoid Hemorrhage

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-005033-53 |
| Trial protocol           | DE CZ FI DK AT |
| Global end of trial date | 22 July 2018   |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 06 December 2018 |
| First version publication date | 06 December 2018 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | EG-01-1962-03 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02790632 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Edge Therapeutics, Inc.  |
| Sponsor organisation address | 300 Connell Dr, Ste 4000, Berkeley Heights, United States, 07922-2817                            |
| Public contact               | Clinical Trial Information, Edge Therapeutics, Inc., 1 9083445257, cdandrea@edgetherapeutics.com |
| Scientific contact           | Clinical Trial Information, Edge Therapeutics, Inc., 1 9083445257, cdandrea@edgetherapeutics.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                       | 06 September 2018 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 22 July 2018      |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 22 July 2018      |
| Was the trial ended prematurely?                     | Yes               |

Notes:

---

**General information about the trial**

Main objective of the trial:

To compare the efficacy of intraventricular EG-1962 to standard of care oral nimodipine in subjects with aneurysmal subarachnoid hemorrhage (aSAH)

Protection of trial subjects:

Subjects were treated in Intensive Care Units

Background therapy: -

Evidence for comparator:

Oral nimodipine is the standard of care treatment for subjects with aSAH.

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 20 June 2016 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

---

**Population of trial subjects****Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 164 |
| Country: Number of subjects enrolled | Hong Kong: 4       |
| Country: Number of subjects enrolled | Australia: 5       |
| Country: Number of subjects enrolled | New Zealand: 8     |
| Country: Number of subjects enrolled | Singapore: 2       |
| Country: Number of subjects enrolled | Canada: 31         |
| Country: Number of subjects enrolled | Israel: 14         |
| Country: Number of subjects enrolled | Austria: 4         |
| Country: Number of subjects enrolled | Czech Republic: 6  |
| Country: Number of subjects enrolled | Finland: 3         |
| Country: Number of subjects enrolled | Germany: 41        |
| Worldwide total number of subjects   | 282                |
| EEA total number of subjects         | 54                 |

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)                     | 215 |
| From 65 to 84 years                      | 67  |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Patients with aneurysmal subarchnoid hemorrhage were recruited at sites located in the United States, Canada, Germany, Austria, Finland, Israel, Singapore, Hong Kong, Australia and New Zealand participated in this study. The study was open for recruitment from June 2016 to March 2018.

### Pre-assignment

Screening details:

318 subjects were consented. 289 subjects were randomized.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Randomization Phase (overall period)                          |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Investigator, Monitor, Data analyst, Subject, Carer, Assessor |

### Arms

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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | EG-1962 |
|------------------|---------|

Arm description: -

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | Intraventricular nimodipine |
| Investigational medicinal product code | EG-1962                     |
| Other name                             |                             |
| Pharmaceutical forms                   | Suspension for injection    |
| Routes of administration               | Intraventricular use        |

Dosage and administration details:

A one-time infusion of EG-1962 was administered intraventricularly following repair of a ruptured saccular aneurysm.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | Placebo Capsules or Tablets |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Suspension for injection    |
| Routes of administration               | Intraventricular use        |

Dosage and administration details:

Subjects received up to 21 days of oral IP per standard of care

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Oral Nimodipine |
|------------------|-----------------|

Arm description: -

|  |                                     |
|--|-------------------------------------|
| Arm type                               | Active comparator                   |
| Investigational medicinal product name | Oral Nimodipine Capsules or Tablets |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Capsule, Tablet                     |
| Routes of administration               | Oral use                            |

Dosage and administration details:

Subjects received oral nimodipine up to 21 days per standard of care.

|  |        |
|--|--------|
| Investigational medicinal product name | Saline |
| Investigational medicinal product code |        |
| Other name                             |        |

|                          |                        |
|--------------------------|------------------------|
| Pharmaceutical forms     | Solution for injection |
| Routes of administration | Intraventricular use   |

Dosage and administration details:

Subjects received a one time intraventricular injection of normal saline.

| <b>Number of subjects in period 1</b> | EG-1962 | Oral Nimodipine |
|---------------------------------------|---------|-----------------|
| Started                               | 138     | 144             |
| Treated                               | 138     | 144             |
| Completed                             | 121     | 128             |
| Not completed                         | 17      | 16              |
| Adverse event, serious fatal          | 10      | 15              |
| Consent withdrawn by subject          | 1       | -               |
| Lost to follow-up                     | 6       | 1               |

## Baseline characteristics

### Reporting groups

|                                |                 |
|--------------------------------|-----------------|
| Reporting group title          | EG-1962         |
| Reporting group description: - |                 |
| Reporting group title          | Oral Nimodipine |
| Reporting group description: - |                 |

| Reporting group values                            | EG-1962  | Oral Nimodipine | Total |
|---|----------|-----------------|-------|
| Number of subjects                                | 138      | 144             | 282   |
| Age categorical<br>Units: Subjects                |          |                 |       |
| Adults  | 138      | 144             | 282   |
| Age continuous<br>Units: years                    |          |                 |       |
| median  | 55.7     | 56.5            |       |
| full range (min-max)                              | 22 to 75 | 30 to 76        | -     |
| Gender categorical<br>Units: Subjects             |          |                 |       |
| Female  | 95       | 42              | 137   |
| Male  | 43       | 102             | 145   |
| WFNS for randomization                            |          |                 |       |
| WFNS entered into IRT for stratification purposes |          |                 |       |
| Units: Subjects                                   |          |                 |       |
| WFNS 1  | 0        | 0               | 0     |
| WFNS 2  | 69       | 69              | 138   |
| WFNS 3/4  | 69       | 75              | 144   |

## End points

### End points reporting groups

|                                   |                 |
|-----------------------------------|-----------------|
| Reporting group title             | EG-1962         |
| Reporting group description: -    |                 |
| Reporting group title             | Oral Nimodipine |
| Reporting group description: -    |                 |
| Subject analysis set title        | GOSE Analysis   |
| Subject analysis set type         | Full analysis   |
| Subject analysis set description: |                 |
| Favorable score is 6, 7 or 8.     |                 |

### Primary: GOSE

|                               |         |
|-------------------------------|---------|
| End point title               | GOSE    |
| End point description:        |         |
| Glasgow Coma Scale - Extended |         |
| End point type                | Primary |
| End point timeframe:          |         |
| Day 90                        |         |

| End point values                 | EG-1962         | Oral Nimodipine |  |  |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type               | Reporting group | Reporting group |  |  |
| Number of subjects analysed      | 135             | 140             |  |  |
| Units: Number of subjects        |                 |                 |  |  |
| number (not applicable)          |                 |                 |  |  |
| 1 - Death                        | 10              | 15              |  |  |
| 2 - Vegetative State             | 2               | 6               |  |  |
| 3 - Lower Significant Disability | 28              | 34              |  |  |
| 4 - Upper Significant Disability | 21              | 16              |  |  |
| 5 - Lower Moderate Disability    | 11              | 11              |  |  |
| 6 - Upper Moderate Disability    | 27              | 20              |  |  |
| 7 - Lower Good Recovery          | 14              | 11              |  |  |
| 8 - Upper Good Recovery          | 23              | 31              |  |  |
| Missing                          | 2               | 0               |  |  |

### Statistical analyses

|                            |                           |
|----------------------------|---------------------------|
| Statistical analysis title | Analysis of GOSE Outcome  |
| Comparison groups          | EG-1962 v Oral Nimodipine |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 275                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.7381 <sup>[1]</sup>        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Mean difference (final values) |

Notes:

[1] - 2-sided p-value

### Secondary: MoCA

|   |           |
|---|-----------|
| End point title   | MoCA      |
| End point description:<br>Montreal Cognitive Assessment |           |
| End point type  | Secondary |
| End point timeframe:<br>Day 90                          |           |

| End point values                                     | EG-1962         | Oral<br>Nimodipine |  |  |
|--|-----------------|--------------------|--|--|
| Subject group type                                   | Reporting group | Reporting group    |  |  |
| Number of subjects analysed                          | 104             | 111                |  |  |
| Units: Number of subjects<br>number (not applicable) |                 |                    |  |  |
| Favorable ( $\geq 26$ )                              | 46              | 51                 |  |  |
| Unfavorable ( $<26$ )                                | 58              | 60                 |  |  |

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs occurring after randomization up to the subject's final visit were recorded

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 19 |
|--------------------|----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | EG-1962 |
|-----------------------|---------|

Reporting group description: -

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Oral Nimodipine |
|-----------------------|-----------------|

Reporting group description: -

| Serious adverse events                            | EG-1962   | Oral Nimodipine   |  |
|---|---|-------------------|--|
| Total subjects affected by serious adverse events |   |                   |  |
| subjects affected / exposed                       | 63 / 138 (45.65%)                                 | 69 / 144 (47.92%) |  |
| number of deaths (all causes)                     | 10  | 15                |  |
| number of deaths resulting from adverse events    | 0   | 0                 |  |
| Nervous system disorders                          |   |                   |  |
| Cerebral Ischaemia                                | Additional description: Delayed Cerebral Ischemia |                   |  |
| subjects affected / exposed                       | 14 / 138 (10.14%)                                 | 18 / 144 (12.50%) |  |
| occurrences causally related to treatment / all   | 0 / 15  | 0 / 19            |  |
| deaths causally related to treatment / all        | 0 / 1   | 0 / 1             |  |
| Hydrocephalus                                     |   |                   |  |
| subjects affected / exposed                       | 17 / 138 (12.32%)                                 | 12 / 144 (8.33%)  |  |
| occurrences causally related to treatment / all   | 0 / 18  | 2 / 12            |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0             |  |
| Cerebral vasoconstriction                         | Additional description: cerebral vasospasm        |                   |  |
| subjects affected / exposed                       | 8 / 138 (5.80%)                                   | 18 / 144 (12.50%) |  |
| occurrences causally related to treatment / all   | 0 / 9   | 0 / 19            |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0             |  |
| Cerebral infarction                               |   |                   |  |
| subjects affected / exposed                       | 9 / 138 (6.52%)                                   | 11 / 144 (7.64%)  |  |
| occurrences causally related to treatment / all   | 0 / 9   | 0 / 12            |  |
| deaths causally related to treatment / all        | 0 / 2   | 0 / 3             |  |

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

| <b>Non-serious adverse events</b>                     | EG-1962  | Oral Nimodipine    |  |
|---|--|--------------------|--|
| Total subjects affected by non-serious adverse events |  |                    |  |
| subjects affected / exposed                           | 136 / 138 (98.55%)                                 | 140 / 144 (97.22%) |  |
| Vascular disorders                                    |  |                    |  |
| Hypertension  |  |                    |  |
| subjects affected / exposed                           | 10 / 138 (7.25%)                                   | 10 / 144 (6.94%)   |  |
| occurrences (all)                                     | 10   | 11                 |  |
| Hypotension   |  |                    |  |
| subjects affected / exposed                           | 9 / 138 (6.52%)                                    | 14 / 144 (9.72%)   |  |
| occurrences (all)                                     | 11   | 17                 |  |
| Nervous system disorders                              |  |                    |  |
| Cerebral vasoconstriction                             | Additional description: cerebral vasospasm         |                    |  |
| subjects affected / exposed                           | 45 / 138 (32.61%)                                  | 51 / 144 (35.42%)  |  |
| occurrences (all)                                     | 46   | 55                 |  |
| Hydrocephalus   |  |                    |  |
| subjects affected / exposed                           | 19 / 138 (13.77%)                                  | 19 / 144 (13.19%)  |  |
| occurrences (all)                                     | 21   | 20                 |  |
| Cerebral ischaemia                                    | Additional description: Delayed Cerebral Ischaemia |                    |  |
| subjects affected / exposed                           | 21 / 138 (15.22%)                                  | 23 / 144 (15.97%)  |  |
| occurrences (all)                                     | 28   | 38                 |  |
| Intracranial Pressure Increased                       |  |                    |  |
| subjects affected / exposed                           | 24 / 138 (17.39%)                                  | 20 / 144 (13.89%)  |  |
| occurrences (all)                                     | 25   | 21                 |  |
| Headache  |  |                    |  |
| subjects affected / exposed                           | 20 / 138 (14.49%)                                  | 14 / 144 (9.72%)   |  |
| occurrences (all)                                     | 23   | 15                 |  |
| Cerebral Infarction                                   |  |                    |  |
| subjects affected / exposed                           | 9 / 138 (6.52%)                                    | 9 / 144 (6.25%)    |  |
| occurrences (all)                                     | 11   | 11                 |  |
| Seizure   |  |                    |  |

|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)   | 12 / 138 (8.70%)<br>12  | 8 / 144 (5.56%)<br>8   |  |
| Cerebral Salt Wasting Syndrome<br>subjects affected / exposed<br>occurrences (all)   | 10 / 138 (7.25%)<br>10  | 16 / 144 (11.11%)<br>16  |  |
| CNS Ventriculitis<br>subjects affected / exposed<br>occurrences (all)  | 8 / 138 (5.80%)<br>8  | 4 / 144 (2.78%)<br>4   |  |
| General disorders and administration<br>site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 45 / 138 (32.61%)<br>49   | 50 / 144 (34.72%)<br>56  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)  | 8 / 138 (5.80%)<br>8  | 14 / 144 (9.72%)<br>25   |  |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)   | 24 / 138 (17.39%)<br>26<br><br>10 / 138 (7.25%)<br>11                             | 29 / 144 (20.14%)<br>30<br><br>11 / 144 (7.64%)<br>11                            |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)<br><br>Agitation<br>subjects affected / exposed<br>occurrences (all)<br><br>Delirium<br>subjects affected / exposed<br>occurrences (all) | 14 / 138 (10.14%)<br>15<br><br>13 / 138 (9.42%)<br>13<br><br>7 / 138 (5.07%)<br>7 | 14 / 144 (9.72%)<br>14<br><br>11 / 144 (7.64%)<br>11<br><br>6 / 144 (4.17%)<br>6 |  |
| Renal and urinary disorders<br>Urinary retention   |   |  |  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 9 / 138 (6.52%)<br>9   | 10 / 144 (6.94%)<br>10   |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)  | 11 / 138 (7.97%)<br>11   | 6 / 144 (4.17%)<br>6   |  |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Pneumonia<br>subjects affected / exposed<br>occurrences (all)   | 37 / 138 (26.81%)<br>42<br><br>23 / 138 (16.67%)<br>24                             | 34 / 144 (23.61%)<br>38<br><br>28 / 144 (19.44%)<br>29                             |  |
| Metabolism and nutrition disorders<br>Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypkalaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all) | 24 / 138 (17.39%)<br>24<br><br>19 / 138 (13.77%)<br>19<br><br>9 / 138 (6.52%)<br>9 | 27 / 144 (18.75%)<br>27<br><br>26 / 144 (18.06%)<br>29<br><br>8 / 144 (5.56%)<br>8 |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

---

### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported