



Clinical trial results:

EFFICACY OF VAS203 IN PATIENTS WITH MODERATE AND SEVERE TRAUMATIC BRAIN INJURY. A confirmatory, placebo-controlled, randomised, double blind, multi-centre study.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-003368-29 |
| Trial protocol | AT ES DE |
| Global end of trial date | 17 June 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 28 June 2021 |
| First version publication date | 28 June 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | VAS203/III/1/04 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02794168 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | vasopharm GmbH |
| Sponsor organisation address | Friedrich-Bergius-Ring 15, Würzburg , Germany, 97076 |
| Public contact | Frank Tegtmeier, vasopharm GmbH, 49 9313590990, tegtmeier@vasopharm.com |
| Scientific contact | Frank Tegtmeier, vasopharm GmbH, 49 9313590990, tegtmeier@vasopharm.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 | 15 July 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 June 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate efficacy of VAS203 on clinical outcome at 6 months (extended Glasgow Outcome Scale Interview, eGOS-I) in patients suffering from moderate and severe traumatic brain injury (TBI)

Protection of trial subjects:

The trial was done in accordance with the good clinical practice guidelines by the International Conference on Harmonisation. As participants were unable to give consent, proxy consent was obtained according local regulations. Consent by the participant was obtained - if possible -as soon as possible.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 01 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 | Spain: 82 |
| Country: Number of subjects enrolled | United Kingdom: 40 |
| Country: Number of subjects enrolled | Austria: 29 |
| Country: Number of subjects enrolled | Germany: 42 |
| Country: Number of subjects enrolled | France: 31 |
| Worldwide total number of subjects | 224 |
| EEA total number of subjects | 184 |

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) | 224 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 38 centres in 5 countries (Austria [3 sites], France [5 sites], Germany [17 sites], Spain [7 sites] and United Kingdom [6 sites]). First Patient First Visit was 24 August 2016), Last Patient Last Visit 17 June 2020.

Pre-assignment

Screening details:

All patients aged from 18 to 60 years with moderate and severe TBI, within 18 hours of injury (but not earlier than 6 hours), which required insertion of an intracranial pressure probe.

Period 1

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

Blinding implementation details:

Appearance of Ronopterin solution differs from that of the placebo (saline). Therefore, infusion solution was prepared by an unblinded team (pharmacy) and provided to the investigators in opaque syringes.

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ronopterin |

Arm description:

Infusion of Ronopterin (VAS203)

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ronopterin |
| Investigational medicinal product code | |
| Other name | VAS203 |
| Pharmaceutical forms | Solution for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

48 hours constant infusion

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

Arm description:

Infusion of Saline

| | |
|--|------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Ronopterin |
| Investigational medicinal product code | |
| Other name | VAS203 |
| Pharmaceutical forms | Solution for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

48 hours constant infusion

| | |
|--|---------------------------------|
| Investigational medicinal product name | Saline |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

48 hours infusion of phosphate buffers saline

| Number of subjects in period 1 | Ronopterin | Placebo |
|---------------------------------------|------------|---------|
| Started | 113 | 111 |
| Completed | 113 | 111 |

Baseline characteristics

Reporting groups

| | |
|--|-------------|
| Reporting group title | Ronopaterin |
| Reporting group description: Infusion of Ronopaterin (VAS203) | |
| Reporting group title | Placebo |
| Reporting group description: Infusion of Saline | |

| Reporting group values | Ronopaterin | Placebo | Total |
|---|----------------|----------------|-------|
| Number of subjects | 113 | 111 | 224 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 39.5 ± 12.4 | 39.1 ± 13.2 | - |
| Gender categorical Units: Subjects | | | |
| Female | 24 | 20 | 44 |
| Male | 89 | 91 | 180 |

End points

End points reporting groups

| | |
|---|------------|
| Reporting group title | Ronopterin |
| Reporting group description: Infusion of Ronopterin (VAS203) | |
| Reporting group title | Placebo |
| Reporting group description: Infusion of Saline | |

Primary: eGOS-I at 6 months after TBI

| | |
|--|------------------------------|
| End point title | eGOS-I at 6 months after TBI |
| End point description: extended Glasgow Outcome Scale | |
| End point type | Primary |
| End point timeframe: 6 months after TBI | |

| End point values | Ronopterin | Placebo | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 112 | 111 | | |
| Units: eGOS categories | | | | |
| 1 - Death | 13 | 11 | | |
| 2 - Vegetative State | 6 | 6 | | |
| 3 - Lower Severe Disability | 15 | 19 | | |
| 4 - Upper Severe Disability | 14 | 7 | | |
| 5 - Lower Moderate Disability | 14 | 18 | | |
| 6 - Upper Moderate Disability | 18 | 21 | | |
| 7 - Lower Good Recovery | 12 | 11 | | |
| 8 - Upper Good Recovery | 20 | 18 | | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Proportional odds-ratio assumption |
| Statistical analysis description: Ordinal Logistic Regression of Patient Overall eGOS-I Rating at 6 Months (Inverse-Normal Approach) | |
| Comparison groups | Ronopterin v Placebo |

| | |
|---|-----------------|
| Number of subjects included in analysis | 223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.388 |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.993 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.627 |
| upper limit | 1.573 |

Post-hoc: Proportion of patients with eGOS-I increase from 3 to 6 months infusion <12h

| | |
|---|--|
| End point title | Proportion of patients with eGOS-I increase from 3 to 6 months infusion <12h |
| End point description: | |
| Number of patients with start of infusion ≤ 12 hours after injury with an increase in extended Glasgow Outcome Score from 3 to 6 months after TBI | |
| End point type | Post-hoc |
| End point timeframe: | |
| Number of patients with an increase of eGOS from 3 to 6 months in patients with start of infusion ≤ 12 hours after TBI. | |

| End point values | Ronopterin | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 | 30 | | |
| Units: Number of patients | 20 | 10 | | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | eGOS-I increase from 3 to 6 months |
| Comparison groups | Ronopterin v Placebo |
| Number of subjects included in analysis | 64 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.039 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.98 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.054 |
| upper limit | 8.426 |

Post-hoc: Proportion of patients with eGOS-I increase from 3 to 6 months infusion >12h

| | |
|--|--|
| End point title | Proportion of patients with eGOS-I increase from 3 to 6 months infusion >12h |
| End point description: Number of patients with start of infusion > 12 hours after injury with an increase in extended Glasgow Outcome Score from 3 to 6 months after injury | |
| End point type | Post-hoc |
| End point timeframe: Number of patients with start of infusion > 12 hours after injury | |

| End point values | Ronopterin | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 76 | 79 | | |
| Units: Number of patients | 24 | 30 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | eGOS-I increase from 3 to 6 months infusion >12h |
| Statistical analysis description: Odds ratios, 95% CIs, and p-values obtained from ordinal logistic regression including treatment group and age group (<40, ≥40) as factors and eGOS-I at 3 months as covariate. | |
| Comparison groups | Ronopterin v Placebo |
| Number of subjects included in analysis | 155 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.431 |
| Method | Regression, Linear |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 1.49 |
| Variability estimate | Standard deviation |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment to Day 14, SAEs from enrollment to 6 months after injury.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 23 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Ronopterin |
|-----------------------|------------|

Reporting group description:

Safety analysis set

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

Reporting group description: -

| Serious adverse events | Ronopterin | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 49 / 113 (43.36%) | 39 / 111 (35.14%) | |
| number of deaths (all causes) | 13 | 11 | |
| number of deaths resulting from adverse events | 13 | 11 | |
| Injury, poisoning and procedural complications | | | |
| Brain contusion | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 2 / 111 (1.80%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 2 / 111 (1.80%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Extradural haematoma | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 2 / 111 (1.80%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain herniation | | | |

| | | | |
|---|-------------------|-----------------|--|
| subjects affected / exposed | 1 / 113 (0.88%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shunt malfunction | | | |
| subjects affected / exposed | 2 / 113 (1.77%) | 0 / 111 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 21 / 113 (18.58%) | 6 / 111 (5.41%) | |
| occurrences causally related to treatment / all | 0 / 21 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 3 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 5 / 113 (4.42%) | 2 / 111 (1.80%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain oedema | | | |
| subjects affected / exposed | 2 / 113 (1.77%) | 3 / 111 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebral haemorrhage | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 113 (0.00%) | 2 / 111 (1.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paroxysmal sympathetic hyperactivity | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain stem ischaemia | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Brain stem infarction | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 0 / 111 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Brain death | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 0 / 111 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Multi-organ disorder | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 0 / 111 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 113 (0.00%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|-----------------|-----------------|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 3 / 113 (2.65%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 113 (1.77%) | 0 / 111 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 6 / 113 (5.31%) | 2 / 111 (1.80%) | |
| occurrences causally related to treatment / all | 6 / 6 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 113 (4.42%) | 2 / 111 (1.80%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 113 (1.77%) | 1 / 111 (0.90%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 113 (1.77%) | 0 / 111 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Emphyema | | | |
| subjects affected / exposed | 1 / 113 (0.88%) | 0 / 111 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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

| Non-serious adverse events | Ronopterin | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 96 / 113 (84.96%) | 93 / 111 (83.78%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 8 / 113 (7.08%) | 8 / 111 (7.21%) | |
| occurrences (all) | 9 | 8 | |
| Nervous system disorders | | | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 27 / 113 (23.89%) | 13 / 111 (11.71%) | |
| occurrences (all) | 32 | 20 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 28 / 113 (24.78%) | 26 / 111 (23.42%) | |
| occurrences (all) | 47 | 57 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 113 (6.19%) | 13 / 111 (11.71%) | |
| occurrences (all) | 9 | 13 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 12 / 113 (10.62%) | 9 / 111 (8.11%) | |
| occurrences (all) | 13 | 9 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 9 / 113 (7.96%) 11 | 4 / 111 (3.60%) 4 | |
| Endocrine disorders Diabetes insipidus subjects affected / exposed occurrences (all) | 6 / 113 (5.31%) 7 | 7 / 111 (6.31%) 11 | |
| Infections and infestations Pneumonia subjects affected / exposed occurrences (all) | 20 / 113 (17.70%) 20 | 22 / 111 (19.82%) 24 | |
| Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all) | 7 / 113 (6.19%) 8 4 / 113 (3.54%) 4 | 11 / 111 (9.91%) 13 8 / 111 (7.21%) 9 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 15 July 2016 | Applicable only for Germany: The protocol was revised to provide details regarding the consenting procedure for vulnerable patients, not capable of giving informed consent prior to enrolment in the clinical study. |
| 05 October 2016 | Applicable only for Germany: amendment provided additional information about the ICF procedure following the Heidelberg Model and the Marburg-Giessen Model |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported