



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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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Reporting groups

Reporting group title	Ronopterin
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Reporting group description:

Safety analysis set

Reporting group title	Placebo
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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