Clinical trial results:
A Multicentre, Randomized, Double-blinded, Placebo-controlled, Parallel Group, Single-dose Design to Determine the Efficacy and Safety of Intravenous NA-1 in Subjects with Acute Ischemic Stroke Undergoing Endovascular Thrombectomy (ESCAPE-NA1 Trial)

Summary

EudraCT number	2016-001826-33
Trial protocol	IE GB DE
Global end of trial date	20 November 2019

Results information

Result version number	v1 (current)
This version publication date	26 November 2020
First version publication date	26 November 2020

Trial information

Trial identification

Sponsor protocol code	NA-1-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02930018
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NoNO Inc.
Sponsor organisation address	479A Wellington Street West, Toronto, Canada, M5V 1E7
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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	28 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2019
Global end of trial reached?	Yes
Global end of trial date	20 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the efficacy of the neuroprotectant, Nerinetide, in reducing global disability in subjects with major AIS with a small established infarct core and with good collateral circulation selected for endovascular revascularization.

Protection of trial subjects:

This study was conducted in substantial compliance with the principles and requirements of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, Canadian Food and Drug Regulations, United States Code of Federal Regulations (CFR; including Title 21 Parts 50, 54, 56, and 312), the Declaration of Helsinki and the Canadian Tri-Council Policy Statement on Ethical Conduct for Research involving Humans (2), where applicable.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2017
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	Australia: 43
Country: Number of subjects enrolled	Canada: 505
Country: Number of subjects enrolled	Germany: 76
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Korea, Republic of: 42
Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 414
Worldwide total number of subjects	1105
EEA total number of subjects	101

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)	398
From 65 to 84 years	578
85 years and over	129

Subject disposition

Recruitment

Recruitment details:

Between 01 March 2017 and 12 August 2019, 1105 subjects were randomized to receive nerinetide or placebo at 48 sites in Canada, US, Germany, Ireland, Sweden, United Kingdom, Australia and the Republic of Korea.

Pre-assignment

Screening details:

Patients with acute ischaemic stroke who were selected to undergo EVT were randomized (1:1) to receive a single intravenous dose of nerinetide (NA-1) or placebo. All patients underwent endovascular thrombectomy and received alteplase in usual care when indicated.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nerinetide (NA-1)

Arm description:

Subjects received a single intravenous infusion of nerinetide over 10 ± 1 minutes.

Arm type	Experimental
Investigational medicinal product name	Nerinetide
Investigational medicinal product code	NA-1
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2.6 mg/kg of active drug (up to a maximum of 270 mg), as a single 10 ±1minute IV infusion.

Arm title	Placebo

Arm description:

Subjects received a single intravenous infusion of placebo over 10 ± 1 minutes.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Phosphate Buffered Saline of equivalent volume given as single 10 ±1minute IV infusion.

Number of subjects in period 1	Nerinetide (NA-1)	Placebo
Started	549	556
Completed	546	550
Not completed	3	6
Consent withdrawn by subject	2	5
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Nerinetide (NA-1)
Reporting group description:	
Subjects received a single intravenous infusion of nerinetide over 10 ± 1 minutes.	
Reporting group title	Placebo
Reporting group description:	
Subjects received a single intravenous infusion of placebo over 10 ± 1 minutes.	

Reporting group values	Nerinetide (NA-1)	Placebo	Total
Number of subjects	549	556	1105
Age categorical Units: Subjects			
Adults (18-64 years)	194	204	398
From 65-84 years	293	285	578
85 years and over	62	67	129
Age continuous Units: years			
median	71.0	70.0	
full range (min-max)	18 to 98	20 to 103	-
Gender categorical Units: Subjects			
Female	268	281	549
Male	281	275	556
Ethnicity(NIH/OMB) Units: Subjects			
Hispanic or Latino	8	15	23
Not Hispanic or Latino	541	540	1081
Unknown or Not Reported	0	1	1
Race(NIH/OMB) Units: Subjects			
Asian	55	52	107
Native Hawaiian or Other Pacific Islander	0	3	3
Black or African American	45	31	76
White	436	453	889
More than one race	0	0	0
Unknown or Not Reported	11	15	26
American Indian or Alaskan Native	2	2	4
Alteplase Treatment			
Treatment with alteplase as part of standard-of-care in addition to study drug			
Units: Subjects			
Subjects treated with alteplase	330	329	659
Subjects not treated with alteplase	219	227	446

End points

End points reporting groups

Reporting group title	Nerinetide (NA-1)
Reporting group description:	
Subjects received a single intravenous infusion of nerinetide over 10 ± 1 minutes.	
Reporting group title	Placebo
Reporting group description:	
Subjects received a single intravenous infusion of placebo over 10 ± 1 minutes.	

Primary: Modified Rankin Score (mRS)

End point title	Modified Rankin Score (mRS)
End point description:	
Overall proportion of subjects experiencing a favorable functional outcome 90 days post-randomization, defined as 0 to 2 on the mRS. The primary hypothesis was that administration of nerinetide (NA-1) would result in an increase in the proportion of responders. The primary analysis was a Wald test for treatment group difference in the primary outcome from a logistic regression adjusted for the 2 stratification variables (alteplase use, first declared thrombectomy device), and the 6 covariates used in the minimization. The trial was designed to have 80% power to detect an 8.7% absolute difference between groups.	
End point type	Primary
End point timeframe:	
90 days	

End point values	Nerinetide (NA-1)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	556		
Units: Subjects	337	329		

Statistical analyses

Statistical analysis title	mRS on ITT population
Comparison groups	Placebo v Nerinetide (NA-1)
Number of subjects included in analysis	1105
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.335 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.146

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.869
upper limit	1.511

Notes:

[1] - Primary outcome was not met in the trial population as a whole, possibly due to a drug-drug interaction between nerinetide and alteplase, as evidenced by a large absolute benefit which was observed for patients who received nerinetide and were not treated with usual care alteplase. The biological plausibility of this hypothesis was supported by pharmacokinetic data obtained from trial participants.
[2] - 2 sided 0.05 significance level

Secondary: National Institutes of Health Stroke Score (NIHSS)

End point title	National Institutes of Health Stroke Score (NIHSS)

End point description:

Proportion of subjects with good neurological outcome, as defined by a score of 0-2 on the NIHSS at Day 90 or the last rating.

End point type	Secondary

End point timeframe:

90 Days or the last rating

End point values	Nerinetide (NA-1)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	556		
Units: Subjects	320	320		

Statistical analyses

Statistical analysis title	NIHSS on ITT Population
Comparison groups	Nerinetide (NA-1) v Placebo
Number of subjects included in analysis	1105
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.866 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.781
upper limit	1.342

Notes:

[3] - Same comment as for the Primary Outcome

[4] - 2 sided 0.05 significance level.

Secondary: Mortality Rate

End point title	Mortality Rate

End point description:

A reduction in mortality rate, as defined by event rate (%) for mortality over the 90-day study period

End point type	Secondary

End point timeframe:

90 Days

End point values	Nerinetide (NA-1)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	556		
Units: Subjects	64	74		

Statistical analyses

Statistical analysis title	Mortality on ITT population
Comparison groups	Nerinetide (NA-1) v Placebo
Number of subjects included in analysis	1105
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.199 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.776
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.527
upper limit	1.143

Notes:

[5] - Same comment as for the Primary Outcome

[6] - 2 sided 0.05 significance level

Post-hoc: Primary Outcome (mRS) in the No-Alteplase Sub-group

End point title	Primary Outcome (mRS) in the No-Alteplase Sub-group

End point description:

Overall proportion of subjects experiencing a favorable functional outcome 90 days post-randomization, defined as 0 to 2 on the mRS in the sub-group of participants not treated with alteplase as part of standard-of-care

End point type	Post-hoc

End point timeframe:

90 days

End point values	Nerinetide (NA-1)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	227		
Units: Subjects	130	113		

Statistical analyses

Statistical analysis title	mRS in the No-Alteplase Sub-group
Comparison groups	Nerinetide (NA-1) v Placebo
Number of subjects included in analysis	446
Analysis specification	Post-hoc
Analysis type	superiority[7]
P-value	= 0.028
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.657
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.055
upper limit	2.603

Notes:

[7] - The unadjusted absolute risk difference in the no-alteplase subgroup was 9.6% (the relative risk difference was 19.3%).

Post-hoc: Primary Outcome (mRS) in the Alteplase Sub-group

End point title	Primary Outcome (mRS) in the Alteplase Sub-group

End point description:

Overall proportion of subjects experiencing a favorable functional outcome 90 days post-randomization, defined as 0 to 2 on the mRS in the sub-group of participants treated with alteplase as part of standard-of-care

End point type	Post-hoc

End point timeframe:

90 days

End point values	Nerinetide (NA-1)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	329		
Units: Subjects	207	216		

Statistical analyses

Statistical analysis title	mRS in the Alteplase group
Comparison groups	Nerinetide (NA-1) v Placebo
Number of subjects included in analysis	659
Analysis specification	Post-hoc
Analysis type	superiority[8]
P-value	= 0.529
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.887
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.612
upper limit	1.286

Notes:

[8] - Treatment effect was not observed in the alteplase group, possibly due to a drug-drug interaction between nerinetide and alteplase, as evidenced by a large absolute benefit which was observed for patients who received nerinetide and were not treated with usualcare alteplase. The biological plausibility of this hypothesis was supported by pharmacokinetic data obtained from trial participants.

Post-hoc: NIHSS in the No-Alteplase Sub-group

End point title	NIHSS in the No-Alteplase Sub-group

End point description:

Proportion of subjects with good neurological outcome, as defined by a score of 0-2 on the NIHSS at Day 90 or the last rating in the sub-group of participants not treated with alteplase as part of standard-of-care

End point type	Post-hoc

End point timeframe:

90 days or last rating

End point values	Nerinetide (NA-1)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	227		
Units: Subjects	129	113		

Statistical analyses

Statistical analysis title	NIHSS in No-Alteplase sub-group
Comparison groups	Placebo v Nerinetide (NA-1)
Number of subjects included in analysis	446
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.088
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.482

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.943
upper limit	2.329

Post-hoc: NIHSS in the Alteplase Sub-group

End point title	NIHSS in the Alteplase Sub-group

End point description:

Proportion of subjects with good neurological outcome, as defined by a score of 0-2 on the NIHSS at Day 90 or the last rating in the sub-group of participants treated with alteplase as part of standard-of-care

End point type	Post-hoc

End point timeframe:

90 days or last rating

End point values	Nerinetide (NA-1)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	329		
Units: Subjects	191	207		

Statistical analyses

Statistical analysis title	NIHSS in the Alteplase sub-group
Comparison groups	Nerinetide (NA-1) v Placebo
Number of subjects included in analysis	659
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.181
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.782
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.545
upper limit	1.121

Post-hoc: Mortality Rate in the No-Alteplase Sub-group

End point title	Mortality Rate in the No-Alteplase Sub-group

End point description:

A reduction in mortality rate, as defined by event rate (%) for mortality over the 90-day study period in the sub-group of participants not treated with alteplase as part of standard-of-care

End point type	Post-hoc

End point timeframe:

90 days

End point values	Nerinetide (NA-1)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	227		
Units: Subjects	25	43		

Statistical analyses

Statistical analysis title	Mortality Rate in the No-Alteplase Sub-group
Comparison groups	Nerinetide (NA-1) v Placebo
Number of subjects included in analysis	446
Analysis specification	Post-hoc
Analysis type	superiority[9]
P-value	= 0.055
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.572
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.323
upper limit	1.013

Notes:

[9] - The unadjusted absolute reduction in mortality rate was 7.5% (relative difference of 39.7%).

Post-hoc: Mortality Rate in the Alteplase Sub-group

End point title	Mortality Rate in the Alteplase Sub-group

End point description:

A reduction in mortality rate, as defined by event rate (%) for mortality over the 90-day study period in the sub-group of participants treated with alteplase as part of standard-of-care

End point type	Post-hoc

End point timeframe:

90 days

End point values	Nerinetide (NA-1)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	329		
Units: Subjects	39	31		

Statistical analyses

Statistical analysis title	Mortality Rate in the Alteplase Sub-group
Comparison groups	Nerinetide (NA-1) v Placebo
Number of subjects included in analysis	659
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.869
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.588
upper limit	1.874

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events occurring within 30 days of randomization and all Serious Adverse Events up to the end of study visit (Day 90 visit or death) or until the subject was deemed "lost to follow-up" were reported.

Adverse event reporting additional description:

Adverse Events of Special Interest (AESI) were collected, and included any Adverse Event occurred within 2 hours of end of drug infusion. Serious Adverse Events (SAEs) exceeding 1% in frequency were reported. SAEs occurred at a frequency of less than 1% (<1%) were grouped and reported as 'All SAEs <1%' in each SOC.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Nerinetide
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Nerinetide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	181 / 547 (33.09%)	198 / 554 (35.74%)	
number of deaths (all causes)	64	73	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
All SAEs <1% Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	5 / 547 (0.91%)	7 / 554 (1.26%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 3	
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 547 (1.28%)	1 / 554 (0.18%)	
occurrences causally related to treatment / all	5 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
All SAEs <1% Vascular disorders			

subjects affected / exposed	11 / 547 (2.01%)	9 / 554 (1.62%)	
occurrences causally related to treatment / all	0 / 11	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
All SAEs <1% Surgical and medical procedures			
subjects affected / exposed	1 / 547 (0.18%)	0 / 554 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
All SAEs <1% General disorders and administration site conditions			
subjects affected / exposed	4 / 547 (0.73%)	10 / 554 (1.81%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
All SAEs <1% Social circumstances			
subjects affected / exposed	0 / 547 (0.00%)	1 / 554 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	19 / 547 (3.47%)	12 / 554 (2.17%)	
occurrences causally related to treatment / all	0 / 19	0 / 12	
deaths causally related to treatment / all	0 / 8	0 / 2	
Pulmonary embolism			
subjects affected / exposed	2 / 547 (0.37%)	6 / 554 (1.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory failure			
subjects affected / exposed	3 / 547 (0.55%)	8 / 554 (1.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 3	0 / 5	
All SAEs <1% Respiratory, thoracic and mediastinal disorders			

subjects affected / exposed	8 / 547 (1.46%)	12 / 554 (2.17%)	
occurrences causally related to treatment / all	0 / 8	1 / 12	
deaths causally related to treatment / all	0 / 4	0 / 8	
Psychiatric disorders			
All SAEs <1% Psychiatric disorders			
subjects affected / exposed	3 / 547 (0.55%)	10 / 554 (1.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
All SAEs <1% Investigations			
subjects affected / exposed	2 / 547 (0.37%)	1 / 554 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
All SAEs <1% Injury, poisoning and procedural complications			
subjects affected / exposed	7 / 547 (1.28%)	21 / 554 (3.79%)	
occurrences causally related to treatment / all	0 / 7	0 / 23	
deaths causally related to treatment / all	0 / 2	0 / 2	
Vascular procedure complication			
subjects affected / exposed	9 / 547 (1.65%)	8 / 554 (1.44%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
All SAEs <1% Congenital, familial and genetic disorders			
subjects affected / exposed	1 / 547 (0.18%)	2 / 554 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
All SAEs <1% Cardiac disorders			
subjects affected / exposed	14 / 547 (2.56%)	12 / 554 (2.17%)	
occurrences causally related to treatment / all	0 / 14	0 / 12	
deaths causally related to treatment / all	0 / 6	0 / 6	
Atrial fibrillation			

subjects affected / exposed	6 / 547 (1.10%)	5 / 554 (0.90%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	9 / 547 (1.65%)	4 / 554 (0.72%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 2	
Myocardial infarction			
subjects affected / exposed	6 / 547 (1.10%)	3 / 554 (0.54%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
All SAEs <1% Nervous system disorders			
subjects affected / exposed	21 / 547 (3.84%)	18 / 554 (3.25%)	
occurrences causally related to treatment / all	1 / 21	1 / 18	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhagic transformation stroke			
subjects affected / exposed	8 / 547 (1.46%)	11 / 554 (1.99%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 4	0 / 7	
Ischaemic stroke			
subjects affected / exposed	18 / 547 (3.29%)	20 / 554 (3.61%)	
occurrences causally related to treatment / all	0 / 18	0 / 20	
deaths causally related to treatment / all	0 / 6	0 / 3	
Stroke in evolution			
subjects affected / exposed	36 / 547 (6.58%)	43 / 554 (7.76%)	
occurrences causally related to treatment / all	1 / 36	0 / 43	
deaths causally related to treatment / all	1 / 27	0 / 32	
Blood and lymphatic system disorders			
All SAEs <1% Blood and lymphatic system disorders			
subjects affected / exposed	2 / 547 (0.37%)	4 / 554 (0.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
All SAEs <1% Eye disorders			
subjects affected / exposed	3 / 547 (0.55%)	3 / 554 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
All SAEs <1% Gastrointestinal disorders			
subjects affected / exposed	10 / 547 (1.83%)	6 / 554 (1.08%)	
occurrences causally related to treatment / all	0 / 10	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Gastrointestinal haemorrhage			
subjects affected / exposed	6 / 547 (1.10%)	4 / 554 (0.72%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
All SAEs <1% Hepatobiliary disorders			
subjects affected / exposed	2 / 547 (0.37%)	3 / 554 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
All SAEs <1% Skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 547 (0.18%)	1 / 554 (0.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
All SAEs <1% Renal and urinary disorders			
subjects affected / exposed	6 / 547 (1.10%)	3 / 554 (0.54%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endocrine disorders			
All SAEs <1% Endocrine disorders			
subjects affected / exposed	1 / 547 (0.18%)	0 / 554 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
All SAEs <1% Musculoskeletal and connective tissue disorders			
subjects affected / exposed	0 / 547 (0.00%)	1 / 554 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
All SAEs <1% Infections and infestations			
subjects affected / exposed	16 / 547 (2.93%)	16 / 554 (2.89%)	
occurrences causally related to treatment / all	0 / 17	0 / 16	
deaths causally related to treatment / all	0 / 5	0 / 4	
Pneumonia			
subjects affected / exposed	6 / 547 (1.10%)	5 / 554 (0.90%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sepsis			
subjects affected / exposed	3 / 547 (0.55%)	6 / 554 (1.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
All SAEs <1% Metabolism and nutrition disorders			
subjects affected / exposed	1 / 547 (0.18%)	2 / 554 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Nerinetide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	474 / 547 (86.65%)	472 / 554 (85.20%)	
Injury, poisoning and procedural complications			
Vascular procedure complication			
subjects affected / exposed	49 / 547 (8.96%)	54 / 554 (9.75%)	
occurrences (all)	54	58	

Vascular disorders			
Hypotension			
subjects affected / exposed	60 / 547 (10.97%)	54 / 554 (9.75%)	
occurrences (all)	61	55	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	48 / 547 (8.78%)	45 / 554 (8.12%)	
occurrences (all)	49	48	
Bradycardia			
subjects affected / exposed	18 / 547 (3.29%)	32 / 554 (5.78%)	
occurrences (all)	18	34	
Nervous system disorders			
Headache			
subjects affected / exposed	79 / 547 (14.44%)	88 / 554 (15.88%)	
occurrences (all)	82	95	
Haemorrhagic transformation stroke			
subjects affected / exposed	60 / 547 (10.97%)	66 / 554 (11.91%)	
occurrences (all)	61	66	
Stroke in evolution			
subjects affected / exposed	48 / 547 (8.78%)	54 / 554 (9.75%)	
occurrences (all)	49	54	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	33 / 547 (6.03%)	42 / 554 (7.58%)	
occurrences (all)	33	45	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	40 / 547 (7.31%)	47 / 554 (8.48%)	
occurrences (all)	41	47	
Vessel puncture site haematoma			
subjects affected / exposed	32 / 547 (5.85%)	28 / 554 (5.05%)	
occurrences (all)	32	29	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	34 / 547 (6.22%)	45 / 554 (8.12%)	
occurrences (all)	34	45	
Nausea			

subjects affected / exposed	37 / 547 (6.76%)	31 / 554 (5.60%)	
occurrences (all)	37	33	
Vomiting			
subjects affected / exposed	31 / 547 (5.67%)	36 / 554 (6.50%)	
occurrences (all)	31	39	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	35 / 547 (6.40%)	28 / 554 (5.05%)	
occurrences (all)	37	33	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	52 / 547 (9.51%)	68 / 554 (12.27%)	
occurrences (all)	52	68	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	33 / 547 (6.03%)	34 / 554 (6.14%)	
occurrences (all)	35	35	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2019	Amendment to protocol included changes which were made in order to address the requests obtained from the German Health Authorities (BfArM) and the applicable ethics committee during their review of the clinical trial application: •Clarifying the specific procedure for inclusion of subjects by the investigator where local regulations and ethics allow (Inclusion Criteria #9 - informed consent). •Clarification to Exclusion Criteria #8 on possible contraindications to iodinated contrast preventing endovascular intervention. •Additional IDMC review at 300 subjects •Removal of the CTA imaging procedure at 2-8 hours in subjects who did not complete a digital subtraction cerebral angiogram, as not standard of care in all regions. •Clarification on maximum dosing to reflect the dosing for subjects weighing 105-120 kg. There is no change to the actual dosing of the drug as used in the trial. •Align Protocol Section 11 (STATISTICS) with the Statistical Analysis Plan •Provide clarification on the conduct of laboratory testing and the collection of pre-morbid mRS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32087818