



Clinical trial results:

A Multicentre, Randomized, Double-blinded, Placebo-controlled, Parallel Group, Single-dose Design to Determine the Efficacy and Safety of Nerinetide in Participants with Acute Ischemic Stroke Undergoing Endovascular Thrombectomy Excluding Thrombolysis (ESCAPE-NEXT Trial)

Summary

EudraCT number	2020-002360-30
Trial protocol	DE NO IT NL
Global end of trial date	19 June 2023

Results information

Result version number	v1 (current)
This version publication date	11 August 2024
First version publication date	11 August 2024
Summary attachment (see zip file)	ESCAPE-NEXT CSR Synopsis (NA-1-009_CSR_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	NA-1-009
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04462536
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NoNO Inc.
Sponsor organisation address	333 Bay Street, Suite 2400, Toronto, Canada, M5H 2T6
Public contact	Yatika Kohli, NoNO Inc., +1 6473092950, ykohli@nonoinc.ca
Scientific contact	Michael Tymianski, NoNO Inc., +1 6472932232, mtymianski@nonoinc.ca

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	13 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2023
Global end of trial reached?	Yes
Global end of trial date	19 June 2023
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 participants with acute ischemic stroke (AIS)

Protection of trial subjects:

Trial was carried out in accordance with the following local requirements in EU: EMEA EudraLex (Volume 4), the Rules Governing Medicinal Products in the European Union, EU Guidelines of Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use and Eudralex (Volume 10), the Rules Governing Medicinal Products in the European Union, Clinical Trials Guidelines 2001/20/EC EU Clinical Trial Directives amended by Regulation (EC) No. 1901/2006 and Regulation (EC) No. 596/2009.

The ICF and the method for obtaining initial and regained capacity consent were approved by the local IEC/IRB prior to their implementation at each clinical site. All methods of conducting the informed consent process complied with ICH GCP E6. Information on how local privacy requirements (e.g., Europe GDPR) were addressed was incorporated as required either as a separate consent or within the ICF. Patient data was pseudo anonymized.

Participants were told that their participation was voluntary, and they could withdraw consent to participate at any time. Each participant or legally authorized representative (LAR) signed and dated an ICF after the nature of the trial had been fully explained and prior to performance of any trial-related activity.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2020
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: 104
Country: Number of subjects enrolled	Germany: 197
Country: Number of subjects enrolled	Netherlands: 49
Country: Number of subjects enrolled	Norway: 18
Country: Number of subjects enrolled	Switzerland: 25
Country: Number of subjects enrolled	Canada: 303
Country: Number of subjects enrolled	Australia: 74
Country: Number of subjects enrolled	Singapore: 20
Country: Number of subjects enrolled	Italy: 60
Worldwide total number of subjects	850
EEA total number of subjects	324

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)	194
From 65 to 84 years	489
85 years and over	167

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Because AIS is a medical emergency, the trial was designed to enable the administration of standard-of-care treatments without delay in order to save the life of the person concerned. Adults ≥ 18 years harboring an AIS who were selected for endovascular revascularization without intravenous (IV) or intra-arterial thrombolytic therapy were enrolled.

Period 1

Period 1 title	Main- 90 days (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

Arms

Are arms mutually exclusive?	Yes
Arm title	Investigational

Arm description:

Nerinetide

Arm type	Experimental
Investigational medicinal product name	Nerinetide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Single dose (2.6 mg/kg) via 10 min IV infusion

Arm title	Control
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Arm description:

Placebo-control arm

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Placebo consisted of the same buffer used for nerinetide with slightly higher NaCl content to adjust for equivalence of osmolality between drug product and placebo. It was supplied in identical 20 mL vials containing 13.5 mL of 50 mL sodium phosphate pH 7.0 (0.55% NaCl).

Number of subjects in period 1	Investigational	Control
Started	454	396
Completed	441	391
Not completed	13	5
Consent withdrawn by subject	9	3
Lost to follow-up	4	2

Baseline characteristics

Reporting groups

Reporting group title	Main- 90 days
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Reporting group description: -

Reporting group values	Main- 90 days	Total	
Number of subjects	850	850	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	73.2		
standard deviation	± 12.96	-	
Gender categorical			
Units: Subjects			
Female	421	421	
Male	429	429	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants randomized into the trial with grouping by randomized treatment, regardless of treatment actually received. Participant grouped according to the randomized (intended) treatment.

Subject analysis set title	safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants randomly assigned to study intervention and who receive any volume of study drug. Participants will be analyzed according to the intervention they actually received.

Reporting group values	ITT	safety	
Number of subjects	850	844	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	73.2	73.2	
standard deviation	± 12.96	± 12.99	
Gender categorical			
Units: Subjects			
Female	421	417	
Male	429	427	

End points

End points reporting groups

Reporting group title	Investigational
Reporting group description: Nerinetide	
Reporting group title	Control
Reporting group description: Placebo-control arm	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants randomized into the trial with grouping by randomized treatment, regardless of treatment actually received. Participant grouped according to the randomized (intended) treatment.	
Subject analysis set title	safety
Subject analysis set type	Safety analysis
Subject analysis set description: All participants randomly assigned to study intervention and who receive any volume of study drug. Participants will be analyzed according to the intervention they actually received.	

Primary: mRS Responder

End point title	mRS Responder
End point description: The proportion of participants with independent functioning on the modified Rankin Scale (mRS), as defined by a score of 0-2 at Day 90 post randomization.	
End point type	Primary
End point timeframe: 90 days post randomization	

End point values	Investigational	Control	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	454	396	850	
Units: subjects				
mRS 0-2	206	181	387	
mRS >2	248	215	463	

Statistical analyses

Statistical analysis title	mRS Responder Analysis
Comparison groups	Investigational v Control

Number of subjects included in analysis	850
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.5
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.959
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.715
upper limit	1.288
Variability estimate	Standard deviation
Dispersion value	0.782

Secondary: Mortality Rate

End point title	Mortality Rate
End point description:	
Mortality rates, defined as the number of deaths observed divided by the number of participants observed over the 90-day study period, were compared between nerinetide- and placebo-treated participants on the ITT population.	
End point type	Secondary
End point timeframe:	
90 days post-randomization	

End point values	Investigational	Control	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	454	396	850	
Units: Subjects				
Death Recorded	87	70	157	
Alive	367	326	693	

Statistical analyses

No statistical analyses for this end point

Secondary: Worsening of Stroke

End point title	Worsening of Stroke
End point description:	
Worsening of stroke was defined as (A) progression or hemorrhagic transformation of the index stroke as documented by medical imaging that was (a) life-threatening (requiring intervention) and/or (b) resulted in increased disability as gauged by a ≥ 4 -point increase from lowest NIHSS during hospitalization OR (B) resulted in death from the index stroke.	
End point type	Secondary

End point timeframe:
90-days post-randomization

End point values	Investigational	Control	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	454	396	850	
Units: Subjects				
worsening of stroke reported	76	68	157	
No worsening of Stroke	378	328	693	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs occurring within 30 days of randomization and all SAEs up to Day 90 visit or death or until the participant was deemed "lost to follow-up" were reported. The safety population included all participants receiving any amount of study drug.

Adverse event reporting additional description:

Frequencies are numbers of subjects experiencing at least one adverse event in that category. Subjects experiencing more than one adverse event in each category are counted only once for that category.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	Nerinetide
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Reporting group description:

Safety assessments in the trial included the frequency of Treatment emergent adverse events (TEAEs), Serious Adverse events (SAEs) and discontinuations due to TEAEs. TEAEs occurring within 30 days of randomization and all SAEs up to the end of study visit (Day 90 visit or death) or until the participant was deemed "lost to follow-up" were reported. The safety population included all participants who received any amount of study drug.

Reporting group title	Placebo
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Reporting group description:

Frequencies are numbers of subjects experiencing at least one adverse event in that category. Subjects experiencing more than one adverse event in each category are counted only once for that category

Serious adverse events	Nerinetide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	182 / 451 (40.35%)	148 / 393 (37.66%)	
number of deaths (all causes)	78	66	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Stroke in evolution			
subjects affected / exposed	29 / 451 (6.43%)	35 / 393 (8.91%)	
occurrences causally related to treatment / all	0 / 29	0 / 35	
deaths causally related to treatment / all	0 / 20	0 / 24	
Ischaemic stroke			
subjects affected / exposed	22 / 451 (4.88%)	14 / 393 (3.56%)	
occurrences causally related to treatment / all	0 / 22	0 / 14	
deaths causally related to treatment / all	0 / 5	0 / 4	
Cerebral haemorrhage			

subjects affected / exposed	8 / 451 (1.77%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 2	
Haemorrhagic transformation stroke			
subjects affected / exposed	8 / 451 (1.77%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Subarachnoid haemorrhage			
subjects affected / exposed	6 / 451 (1.33%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	0 / 6	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	6 / 451 (1.33%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 5	0 / 1	
Seizure			
subjects affected / exposed	5 / 451 (1.11%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery dissection			
subjects affected / exposed	3 / 451 (0.67%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	1 / 451 (0.22%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 451 (0.22%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			

subjects affected / exposed	13 / 451 (2.88%)	12 / 393 (3.05%)	
occurrences causally related to treatment / all	0 / 13	0 / 12	
deaths causally related to treatment / all	0 / 7	0 / 5	

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

Non-serious adverse events	Nerinetide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	393 / 451 (87.14%)	337 / 393 (85.75%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	54 / 451 (11.97%)	36 / 393 (9.16%)	
occurrences (all)	54	36	
Cardiac disorders			
Atrial fibrillation	Additional description: Frequencies are numbers of subjects experiencing at least one adverse event in that category. Subjects experiencing more than one adverse event in each category are counted only once for that category		
subjects affected / exposed	30 / 451 (6.65%)	17 / 393 (4.33%)	
occurrences (all)	30	17	
Nervous system disorders			
Haemorrhagic transformation stroke			
subjects affected / exposed	58 / 451 (12.86%)	42 / 393 (10.69%)	
occurrences (all)	58	42	
headache			
subjects affected / exposed	52 / 451 (11.53%)	26 / 393 (6.62%)	
occurrences (all)	52	26	
Stroke in evolution	Additional description: Frequencies are numbers of subjects experiencing at least one adverse event in that category. Subjects experiencing more than one adverse event in each category are counted only once for that category.		
subjects affected / exposed	40 / 451 (8.87%)	37 / 393 (9.41%)	
occurrences (all)	40	37	
Ischaemic stroke	Additional description: Frequencies are numbers of subjects experiencing at least one adverse event in that category. Subjects experiencing more than one adverse event in each category are counted only once for that category		
subjects affected / exposed	27 / 451 (5.99%)	22 / 393 (5.60%)	
occurrences (all)	27	22	
General disorders and administration site conditions			
Pyrexia	Additional description: Frequencies are numbers of subjects experiencing at least one adverse event in that category. Subjects experiencing more than one adverse event in each category are counted only once for that category		

subjects affected / exposed occurrences (all)	35 / 451 (7.76%) 35	36 / 393 (9.16%) 36	
Gastrointestinal disorders Constipation	Additional description: Frequencies are numbers of subjects experiencing at least one adverse event in that category. Subjects experiencing more than one adverse event in each category are counted only once for that category		
subjects affected / exposed occurrences (all)	36 / 451 (7.98%) 36	22 / 393 (5.60%) 22	
Psychiatric disorders Delirium	Additional description: Frequencies are numbers of subjects experiencing at least one adverse event in that category. Subjects experiencing more than one adverse event in each category are counted only once for that category		
subjects affected / exposed occurrences (all)	26 / 451 (5.76%) 26	25 / 393 (6.36%) 25	
Infections and infestations Urinary tract infection			
subjects affected / exposed occurrences (all)	52 / 451 (11.53%) 52	46 / 393 (11.70%) 46	
Metabolism and nutrition disorders Hypokalaemia			
subjects affected / exposed occurrences (all)	47 / 451 (10.42%) 47	34 / 393 (8.65%) 34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2021	- Updated Primary Analysis to adjust for Covariates - altered the hierarchical testing order - to remove collection of immunogenicity samples
01 June 2022	- Adaptive sample re-estimation design to more traditional group sequential design - provide clarification of the handling of intercurrent events

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported