

HEALTH TECHNOLOGY BRIEFING MAY 2019

Nerinetide for acute ischaemic stroke

NIHRIO ID	8308	NICE ID	10074
Developer/Company	NoNO Inc	UKPS ID	Not available

Licensing and market availability plans	Currently in phase III clinical trials.
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SUMMARY

Nerinetide is in clinical development for the treatment of acute ischaemic stroke. Ischaemic stroke is the most common type of stroke. It happens when a blood vessel is blocked by a blood clot, cutting off blood flow to part of the brain (ischaemia). Without blood supply, brain cells can be damaged or destroyed because they may not receive enough oxygen. Symptoms may include numbness or weakness on one side of the body and problems with balance, speech and swallowing. Symptoms may range from mild and resolve, through severe strokes that can lead to long-term disability, coma and death. Early treatment is critical to improve outcomes and aims to restore blood flow to the brain, prevent and possibly repair the damage. Current therapies address only the restoration of blood flow, but not protection of the brain by enhancing its resilience to ischaemia.

Nerinetide is an innovative new drug that protects the brain during an acute ischaemic stroke. As a neuroprotectant, nerinetide does not dissolve blood clots, but effectively pauses the toxic chemical reactions triggered by stroke. Treatment with nerinetide is being positioned to be initiated as soon as possible after the onset of symptoms. If licensed, nerinetide would provide critical time to patients with a stroke by stopping the loss of brain cells until further treatment can be administered.

PROPOSED INDICATION

Acute ischaemic stroke (AIS) – treatment to be initiated as soon as possible after symptom onset^a

TECHNOLOGY

DESCRIPTION

Nerinetide (NA-1; Tat-NR2B9c) is an interfering peptide (IP) and acts by uncoupling postsynaptic density-95 protein (PSD-95), an abundant protein in synapses, from N-methyl-D-aspartate receptors (NMDARs) and other neurotoxic signalling proteins including nitric oxide (NO) synthase (nNOS). PSD-95 links NMDARs to these toxic downstream cascades including nNOS, and uncoupling this link reduces the effectiveness of neurotoxic signalling through NMDARs. The relevant protein-protein interactions of PSD-95 which are the target of nerinetide are those forming a complex binding PSD-95 to both the C-terminus (tSXV domain) of NMDAR GluN2 subunits and to the PDZ domain of nNOS. Disrupting NMDAR-PSD-95-nNOS complexes with nerinetide reduces the efficiency by which calcium ions (Ca²⁺) activate excitotoxic NO production via nNOS. This occurs without blocking normal synaptic function of NMDARs or calcium influx, thus preventing neuronal cell death without blocking synaptic activity.¹

In the phase III clinical trial (NCT02930018; ESCAPE-NA1) patients receive a single intravenous (IV) infusion of nerinetide 2.6 mg/kg over 10 ± 1 minutes.²

INNOVATION AND/OR ADVANTAGES

There are very few treatments that have been shown to be beneficial in acute stroke. Recent findings have provided insights into the pathophysiology and mechanisms of ischaemic stroke, complementing the traditional glutamate hypothesis: the molecular interaction between PSD-95 and GluN2B has been identified as a culprit in stroke-mediated excitotoxicity, leading to the discovery of nerinetide, a peptide that disrupts that interaction, as a potent neuroprotective agent for the treatment of acute stroke.¹

Currently, the main treatment for acute stroke is thrombolysis, which is indicated within approximately 4.5 hours from stroke symptom onset. Thrombolysis is typically accomplished by the administration of tissue plasminogen activator (tPA). However, not all patients with a stroke are candidates for thrombolysis. In fact, due to the risk of haemorrhagic stroke (and bleeding in general), there are strict eligibility criteria for tPA administration.¹ Medical imaging and the time required to qualify patients for recanalization can also be a barrier to rapid treatment and optimal outcomes.³ Nerinetide, given its safety profile, is also being investigated in stroke patients prior to medical imaging and has been studied in haemorrhagic patients.⁴

Therefore, because of the rapidly progressive nature of acute stroke, the lack of early pharmacological interventions (besides tPA) and the absence of treatments to promote recovery leave many patients with long-term disabilities. Thus, there is a significant unmet medical need to develop additional treatments for stroke, such as neuroprotectants: drugs that reduce the vulnerability of the brain to ischaemia.¹

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nerinetide is not currently licensed for any indication in the EU/UK.

^a Information provided by NoNO Inc

Nerinetide is in phase III clinical development for suspected stroke.^{4,5} A phase II study in procedurally induced stroke and subarachnoid haemorrhage has also been completed.⁶

Nerinetide is an orphan drug in the USA in 2014 for the treatment of acute ischaemic stroke patients presenting within 3 hours of symptom onset.⁷ Nerinetide has also been granted Fast-Track Designation by the US FDA in 2012 for the reduction of procedurally induced strokes and cognitive impairment in patients undergoing endovascular repair of brain aneurysms.⁸

PATIENT GROUP

DISEASE BACKGROUND

A stroke is a serious life-threatening medical condition that occurs when the blood supply to part of the brain is cut off.⁹ An acute stroke refers to the first 24-hour-period of a stroke event.¹⁰ There are two main types of stroke: ischaemic strokes, caused by blockages which cut off the blood supply to parts of the brain, and haemorrhagic strokes, which are caused when a blood vessel bursts within or on the surface of the brain. Approximately 85% of all strokes are ischaemic and 15% are haemorrhagic.¹¹ There is also a related condition known as transient ischaemic attack (TIA), where the blood supply to the brain is temporarily interrupted.⁹

Depending on the severity of the ischemia, infarction (cellular death) will occur within minutes, causing irreversible damage even after blood flow is restored. This is called the “core” of the infarct. Surrounding the core is tissue that is affected but functionally that may recover if blood flow is restored. This is called the “ischaemic penumbra”. Most people will have such an ischaemic penumbra amenable to treatment within the first 3 hours of occlusion of the cerebral artery, but many patients may have brain left to save even at 24 hours.^{10,12}

Stroke is most commonly manifested by focal neurological deficits such as numbness or weakness of the face, arm or leg on one side of the body, and often problems with speech and swallowing.^{13,14} Certain conditions increase the risk of having a stroke including high blood pressure (hypertension), high cholesterol, atrial fibrillation, and diabetes.⁹ Other risk factors may include smoking, age and gender, race and ethnicity, a personal or family history of stroke or TIA, and brain aneurysms or arteriovenous malformations.¹⁵ As of 2017, the average age of stroke in England, Wales and Northern Ireland was 72 years for men and 78 years for women.^{11,16}

With improvements in health care, more people survive stroke but many have to cope with the physical, psychological, social and functional sequelae, resulting in increased personal and public costs. Stroke causes a significant deterioration of the patient’s functioning and worsening of her/his quality of life. Long-term disability caused by stroke is a common problem in all countries and its incidence increases markedly with advancing age.¹⁷

CLINICAL NEED AND BURDEN OF DISEASE

There are more than 100,000 strokes in the UK each year. This figure may be higher, as available data relies on hospital admission and does not include deaths before reaching hospital, or those who were not treated in hospital.¹¹

Approximately 1 in 6 men and 1 in 5 women will have a stroke in their life.^{11,18} The rate of first time strokes in people aged 45 years and over is expected to increase in the UK by 59% between 2015 and 2035. In the same period, it is estimated that the number of stroke survivors, aged 45 years and over, living in the UK is expected to rise by 123%.^{11,19} It is estimated the number of UK stroke patients eligible for endovascular thrombectomy ranges between 10-12%.^{20,21}

Stroke survivors are at greatest risk of having another stroke in the first 30 days following the initial occurrence.^{11,19} Approximately 1 in 4 stroke survivors will experience another stroke within five years.⁷ Hospital admissions data for England in 2017-2018 recorded 142,963 finished consultant episodes (FCE) for cerebral infarction (ICD-10 code: 163), 71,568 hospital admissions and 159 day cases.²²

In 2015, the average societal cost of stroke per person was £45,409 in the first 12 months after stroke (cost of incident stroke), plus £24,778 in subsequent years (cost of prevalent stroke). It is projected that the overall costs of stroke in the UK for those aged 45 years and over will rise from £26 billion in 2015 to £43 billion in 2025 and £75 billion in 2035, an increase of 194% over 20 years.²³

Stroke is a leading cause of death and disability in the UK.²⁴ In 2016 there were a total of 32,627 deaths from stroke in England and Wales.⁷

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The primary aim of stroke therapy is to restore blood flow to the brain in a manner that does not exacerbate the damage already caused by depriving the tissue of oxygen and nutrients. The secondary aim is to modulate any factors that may exacerbate this damage and if possible, repair the damage.²⁵ Early treatment is critical to rescue potentially salvageable tissue.²⁶

Patients suspected of having an AIS should have rapid assessment and early intervention with specialist care. Recanalisation strategies, such as thrombolysis, attempt to re-establish blood flow so that cells starved of oxygen can be rescued before they are irreversibly damaged. Mechanical clot retrieval (endovascular thrombectomy) for treating AIS aims to remove the obstructing blood clot or other material from arteries within the brain, restoring blood flow to the brain and minimising brain tissue damage.¹⁴

Currently, the main treatment (pharmacological) for acute stroke is thrombolysis, which is indicated within approximately 4.5 hours from stroke symptom onset. Thrombolysis is typically accomplished by the administration of tPA.²⁷

CURRENT TREATMENT OPTIONS

Alteplase is a recombinant human tissue-type plasminogen activator, recommended within its marketing authorisation for treating AIS in adults if:²⁷

- treatment is started as early as possible within 4.5 hours of onset of stroke symptoms, and intracranial haemorrhage has been excluded by appropriate imaging techniques

PLACE OF TECHNOLOGY

If licensed, nerinetide may offer AIS patients improved functional outcomes by 1) preventing excitotoxic neuronal cell death due to ischaemia and preserving brain tissue, and 2) providing critical additional time for reperfusion therapy to restore blood flow.

CLINICAL TRIAL INFORMATION

Trial	ESCAPE-NA1, NCT02930018 , EudraCT2016-001826-33; nerinetide vs placebo; phase III
Sponsor	NoNO Inc.
Status	Ongoing
Source of Information	Trial registry ²⁸ , trial protocol ²
Location	4 EU countries (incl UK), USA, Canada, Australia and South Korea
Design	Randomised, double-blind, placebo-controlled, parallel group, single-dose design
Participants	n=1120 (planned); AIS for immediate endovascular treatment; ≥18 years of age; onset (last-seen-well) time to randomisation time within 12 hours
Schedule	Subjects are randomised 1:1 to receive 2.6 mg/kg of nerinetide or matching normal saline placebo volume administered as a single 10 ± 1 minute IV in the upper or lower extremity using an infusion pump starting after randomization. All subjects will undergo attempted endovascular recanalization therapy with the intended endovascular approach being either using a stent retriever or clot aspiration device and receive best medical care according to modern acute stroke care guidelines.
Follow-up	This study consists of one 90-day study period for each subject. Subjects will be hospitalised for care after their acute stroke according to the current standard of care.
Primary Outcomes	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 rapid endovascular revascularisation.
Secondary Outcomes	The secondary objectives are to determine the efficacy of nerinetide in: <ul style="list-style-type: none"> • Reducing functional dependence • Improving neurological outcome • Improving activities of daily living • Reducing mortality rate The leading safety objectives are to determine the effect of administering a dose of 2.6 mg/kg IV) of nerinetide to subject with acute stroke who are selected for endovascular revascularisation on serious adverse events (SAEs) and 90-day mortality.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary and study completion date reported as Apr 2020.

ESTIMATED COST

The cost of nerinetide is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Alteplase for treating acute ischaemic stroke (TA264). September 2012.
- NICE clinical guideline. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management (CG68). July 2008. Updated March 2017.
- NICE interventional procedure guidance in development. Therapeutic hypothermia following ischaemic stroke (GID-IPG10092). Expected date of issue to be confirmed.
- NICE interventional procedure guidance. Mechanical clot retrieval for treating acute ischaemic stroke (IPG548). February 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. Service Specifications: Specialised Vascular Services (Adults). 170004/S.
- NHS England. Clinical Commissioning Policy: Mechanical thrombectomy for acute ischaemic stroke (all ages). 170033P. March 2018.

OTHER GUIDANCE

- NICE medtech innovation briefing. Mechanical thrombectomy devices for acute ischaemic stroke (MIB153). July 2018²¹
- Royal College of Physicians. National clinical guideline for stroke: 5th edition. 2016²⁹

ADDITIONAL INFORMATION

NoNO Inc. did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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