

NoNO Inc. Reports Groundbreaking Results from the Phase 3 ESCAPE-NA1 Study of the Peptide, Nerinetide, in Acute Ischemic Stroke

- The novel peptide nerinetide, without prior administration of alteplase, improved functional outcome, reduced mortality and reduced infarct volume among acute ischemic stroke patients
- Data presented at the plenary session of the International Stroke Conference 2020 and simultaneously published online in The Lancet

TORONTO, Feb. 20, 2020 (GLOBE NEWSWIRE) -- NoNO Inc., a privately-held biotechnology company, today reported results from the pivotal Phase 3 ESCAPE-NA1 study, a multicenter, randomized, double-blinded, placebo-controlled, parallel group, single-dose study to evaluate the efficacy and safety of intravenous administration of the novel peptide, nerinetide, in patients with acute ischemic stroke who were selected to undergo endovascular thrombectomy. Nerinetide, without prior administration of alteplase, showed medically important improvements in patients with acute ischemic stroke. The ESCAPE-NA1 results were presented at the International Stroke Conference in Los Angeles and published simultaneously online in the peer-reviewed journal *The Lancet*.

"Results of the ESCAPE-NA1 Phase 3 clinical trial are scientifically groundbreaking because it demonstrates important effects of a pharmaceutical therapy in an acute stroke population treated for up to 12 hours after stroke symptom emergence," said Dr. Michael Tymianski, president and chief executive officer and founder of NoNO Inc. "Although patients who had prior administration of alteplase did not appear to benefit, likely due to a reduction of nerinetide plasma levels when alteplase was given first, we are excited by the magnitude and consistency of data in the pre-specified subgroup that were not treated with alteplase as well as the potentially long therapeutic window of nerinetide after stroke onset. In addition, nerinetide was well tolerated."

Study Design

The ESCAPE-NA1 Phase 3 clinical trial is the largest study of patients selected for endovascular thrombectomy (EVT) conducted to date enrolling 1,105 patients across 48 sites globally including the U.S., Canada, EU, Asia and Australia. Participants were randomized to either a single 2.6 mg/kg dose of nerinetide or placebo immediately following meeting of enrollment criteria, which included enrolling participants within a 12-hour window from stroke onset to randomization, and within 30 minutes of randomization. Alteplase was administered to a subset of patients as per standard of care. The enrolled patient population was stratified into two pre-specified subgroups – patients treated with alteplase and patients not treated with alteplase – because of prior data that showed that alteplase activates plasmin, which cleaves nerinetide and can reduce its plasma levels and thus its potential for efficacy. The primary endpoint was the proportion of patients who achieve functional independence at 90 days after their stroke, defined as 0-2 on the Modified Rankin Scale (mRS; range 0 to 6, with higher scores indicating greater disability). Additional outcomes were other measures of neurological disability, mortality, and measurements of stroke volume by medical imaging. Safety was monitored throughout the 90-day observation period for each participant. Additional analyses were conducted for subjects who had received, or not received, alteplase. The study was co-led by Michael Hill, M.D., a neurologist at Foothills Medical Centre (FMC) and professor in the departments of Clinical Neurosciences and Radiology at the Cumming School of Medicine (CSM), University of Calgary and Mayank Goyal, M.D., Ph.D., a neuroradiologist at the FMC, and clinical professor in the Department of Radiology at the CSM, University of Calgary.

Results

Analysis of the primary endpoint of the proportion of patients who achieve functional independence after 90 days across all trial participants (those not receiving alteplase and those who received alteplase before nerinetide) did not reach statistical significance (see table). No participant in this study received alteplase after nerinetide. Patients who did not receive alteplase showed medically important improvements in functional independence, reduced mortality, and reduced infarction volumes vs. placebo.

Group	% Reaching Functional Independence			Infarct Volume	Mortality	Nerinetide C _{max}
	Nerinetide (n/N)	Placebo (n/N)	P value	% Chg. vs. Placebo	% Chg. Vs. Placebo	(% of no- alteplase)
All patients	61.4% (337/549)	59.2% (329/556)	P=0.335	No difference (p=0.221)	No difference (p=0.285) **	N/A
Prior alteplase*	62.7% (207/330)	65.7% (216/329)	P=0.529	No difference (p=0.967)	No difference (p=0.544)	39.6%
No alteplase	59.4% (130/219)	49.8% (113/227)	P=0.028	-22% (p=0.048)	-40% (p=0.034) **	100%

n = number meeting endpoint, N = total number in subgroup, ** unadjusted statistic, with missing data (9 total in trial) imputed to death.

*Outcomes between the alteplase and no alteplase participants cannot be compared as they are different populations. Patients who received alteplase were generally enrolled within a window corresponding to the alteplase treatment guidelines (up to 4.5 hours from symptom onset) whereas participants in the no-alteplase group were enrolled over the 12 hour window dictated by the trial protocol.

These findings, which were consistent over three different domains of clinical outcome in patients who did not receive alteplase were bolstered further by pharmacokinetic data from trial participants showing that patients who were treated with alteplase had an approximately 60% reduction in plasma nerinetide levels as compared with patients who did not receive alteplase. Separate non-clinical studies by NoNO Inc. have shown that prior alteplase administration can lower plasma nerinetide concentrations because alteplase activates plasmin, an enzyme that cleaves nerinetide.

Nerinetide had a safety profile comparable to placebo.

“Compared to placebo, almost 20 per cent more patients who received nerinetide along with endovascular treatment, but did not receive alteplase, recovered from a devastating stroke – a difference between paralysis and walking out of the hospital,” said Michael Hill, M.D., one of the ESCAPE-NA1 global coordinating investigators. “In the patients who received both drugs, the alteplase negated the benefits of the nerinetide.

“The study provides evidence of the validity of a biological pathway that protects brain cells from dying when they are deprived of blood flow. Nerinetide targets a protein in brain cells called PSD-95 which links the deprivation of blood flow to signals that mediate the final stage of the brain cell’s life. It does so by stopping the production of the free radical nitric oxide within the cell. Images of patients’ brains from the study show the expected size of the damage from the stroke is reduced when nerinetide is administered and EVT is performed among patients not concurrently receiving alteplase. We really believe this is a new scientific observation. There is evidence nerinetide promotes brain cell survival, offering neuroprotection until we can extract the clot. It opens the door to a new way of treating stroke.”

NoNO Inc. are conducting further studies of nerinetide including an ongoing pivotal trial called FRONTIER.

“FRONTIER could provide important confirmation of the effects of nerinetide seen in ESCAPE-NA1, as well as its effectiveness when it is given before alteplase,” said Dr. Tymianski. “Patients in FRONTIER, who are enrolled with suspected strokes by paramedics in the field, are treated with nerinetide in the ambulance prior to arrival to the stroke hospital and before alteplase would be administered. This should allow nerinetide to reach neurons before it is impacted by alteplase. FRONTIER may provide evidence for the benefits of nerinetide in even broader stroke populations, and complements ESCAPE-NA1 as we seek to provide future patients with opportunities for a better life.”

About the University of Calgary

The University of Calgary is a global intellectual hub located in Canada’s most enterprising city. In our spirited, high-quality learning environment, students thrive in programs made rich by research, hands-on experiences and entrepreneurial thinking. Our strategy drives us to be recognized as one of Canada’s top five research universities, engaging the communities we both serve and lead. This strategy is called *Eyes High*, inspired by the university's Gaelic motto, which translates as 'I will lift up my eyes.' For more information, visit ucalgary.ca/eyeshigh.

About NoNO Inc.

NoNO Inc. is an Ontario biotechnology company whose focus is on developing therapeutic drugs in areas of unmet medical needs. Its drug pipeline includes therapeutic agents in various stages of development ranging from cellular and molecular discovery to human clinical trials. Its lead projects relate to diseases of the nervous system whose mechanisms involve the protein PSD-95, including stroke, traumatic brain injury and neuropathic pain. NoNO Inc.'s strategy is to inhibit key protein-protein interactions of PSD-95 that are involved selectively in cellular signals that cause cell damage, but without interfering with normal cell functions. For more information, please visit www.nonoinc.ca.

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