ESCAPE-NA1 trial

ESCAPE-NA1 Investigators
Statement of funding and disclosures

• The trial was funded by:
  • Canadian Institutes for Health Research
  • Alberta Innovates
  • NoNO Inc.

• NoNO Inc was the regulatory sponsor for the trial, provided study drug, and monitored regulatory compliance of the study

• The trial was organized as an academic-industry collaboration and coordinated at the University of Calgary
Background

• Publications of over 1000 treatments, largely neuroprotectants, have shown promise in pre-clinical models of ischemic stroke

• A smaller percentage (~10%) have been studied in human clinical trials, but no neuroprotectants have shown a clinical benefit

• Nerinetide (NA-1; Tat-NR2B9c) is a promising agent that has shown neuroprotection in cell cultures, rodents, primates and in a phase 2 study in humans undergoing endovascular repair of intracranial aneurysms*

*Hill et al., Lancet Neurol. 2012;11:942-950
Nerinetide reduces infarct volume in Cynomolgous macaques subjected to ischemia-reperfusion*

Nerinetide improves neurological function in a range of behavioral tests*

Two Tube Test

6 Well Test

Hill/Valley tests

“Shift” on NIHPSS suggests that neuroprotection can improve function on top of reperfusion (cOR = 8.19)

Adapted from data in:
Study Design

ESCAPE-NA1 aimed to recapitulate the primate model in community-onset ischemic stroke, accounting for existing standards of care including alteplase.

- Phase 3, multicentre, blinded, placebo-controlled, parallel group, single-dose design.
- Up to 1120 male and female subject will be enrolled.
- Randomization 1:1 nerinetide to placebo, stratified by alteplase use and by declared first choice of device.
Inclusion Criteria

1. Acute ischemic stroke (AIS) for immediate endovascular treatment.
2. Age 18 or greater.
3. Onset (last-seen-well) time to randomization time within 12 hours.
4. Disabling stroke defined as a baseline NIHSS > 5 at the time of randomization.
5. Pre-stroke (24 hours prior to stroke onset) independent functional status in activities of daily living with modified Barthel Index (BI) > 90 (95 or 100). Patient must be living in their own home, apartment or seniors lodge where no nursing care is required.
Imaging criteria

• CT head: ASPECTS >= 5 (exclude large core)

• mCTA: ICA + M1 or M1 or functional M1 (all M2s)

• mCTA: moderate to good collaterals
Intervention

• Single, ten minute infusion of 2.6 mg/kg intravenous dose of nerinetide or (saline) placebo as soon as enrollment criteria met, and started within 30 minutes of randomization.

• All patients had EVT

• Patients received intravenous alteplase according to current stroke guidelines (best medical management)
48 ESCAPE-NA1 Sites
Nerinetide did not significantly improve functional independence in the entire trial population

Overall Results: 1105 (Alteplase and No-Alteplase combined)

ESCAPE-NA1: overall result (n=1105)

<table>
<thead>
<tr>
<th>90-day mRS</th>
<th>Placebo</th>
<th>Nerinetide</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19.1</td>
<td>15.1</td>
</tr>
<tr>
<td>10</td>
<td>21.6</td>
<td>25.3</td>
</tr>
<tr>
<td>20</td>
<td>18.5</td>
<td>20.9</td>
</tr>
<tr>
<td>30</td>
<td>10.8</td>
<td>11.5</td>
</tr>
<tr>
<td>40</td>
<td>6.5</td>
<td>7.5</td>
</tr>
<tr>
<td>50</td>
<td>9.2</td>
<td>7.5</td>
</tr>
<tr>
<td>60</td>
<td>14.4</td>
<td>12.2</td>
</tr>
<tr>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
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</tbody>
</table>

NA-1: 61.3%, Placebo: 59.2%, Absolute Risk Difference: 2.1%; adj RR = 1.04 (0.96 to 1.14); p=0.350
Effect modification (interaction) by alteplase treatment

IV alteplase (n=659) v No IV alteplase (n=446)

P(interaction) = 0.0330, on binary outcome mRS 0-2
No Alteplase stratum

Effect size on mRS 0-2:
• 9.5% absolute risk difference
• Adj RR = 1.18 (1.01 to 1.38)

Mortality reduction:
• 7.5% absolute risk difference

Infarct volume reduction
• 39.2 vs. 26.7 ml (median)
Mortality Benefit in the no-alteplase stratum

Mortality reduction:
- 7.5% absolute risk difference
- Adj HR = 0.56 (0.34-0.95)

Cox proportional hazards regression
No Alteplase Grp: ESCAPE-NA1 (n=446)

Survival vs. Time in days

HR = 0.56, CI95 0.34-0.95, p=0.030, Adjusted: age, sex, NIHSS, ASPECTS, occlusion loc, glc
Large reduction in nerinetide levels (red line) in the alteplase group
Safety events were similar in both groups

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=554)</th>
<th>Nerinetide (n=547)</th>
<th>RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious adverse event</td>
<td>198 (35.7%)</td>
<td>181 (33.1%)</td>
<td>0.92 (0.79-1.09)</td>
</tr>
<tr>
<td>Stroke-in-evolution (progression)</td>
<td>43 (7.8%)</td>
<td>36 (6.6%)</td>
<td>0.85 (0.55-1.30)</td>
</tr>
<tr>
<td>Ischaemic stroke (new onset/recurrent)</td>
<td>20 (3.6%)</td>
<td>18 (3.3%)</td>
<td>0.91 (0.49-1.70)</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>24 (4.3%)</td>
<td>19 (3.5%)</td>
<td>0.80 (0.44-1.45)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17 (3.1%)</td>
<td>25 (4.6%)</td>
<td>1.49 (0.81-2.73)</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>4 (0.7%)</td>
<td>9 (1.6%)</td>
<td>2.28 (0.71-7.36)</td>
</tr>
<tr>
<td>Hypotension**</td>
<td>1 (0.2%)</td>
<td>7 (1.3%)</td>
<td>7.09 (0.88-57.4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (1.3%)</td>
<td>8 (1.5%)</td>
<td>1.15 (0.42-3.17)</td>
</tr>
<tr>
<td>Deep vein thrombosis/ pulmonary embolism</td>
<td>8 (1.4%)</td>
<td>3 (0.5%)</td>
<td>0.38 (0.1-1.42)</td>
</tr>
<tr>
<td>Angioedema</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1.01 (0.06-16.1)</td>
</tr>
<tr>
<td>Hives/Urticaria/Pruritis</td>
<td>0</td>
<td>0</td>
<td>---</td>
</tr>
</tbody>
</table>
Summary

• Including all patients, nerinetide was not superior to placebo (2.1% effect size)
• However, effect modification by alteplase was present
• In the no alteplase stratum,
  • 9.5% absolute effect size in the nerinetide group [adjRR 1.18 (1.01-1.38)]
  • 12.5 cc reduction in median infarct volume
  • 7.5% absolute mortality benefit [adjHR 0.56 (0.34-0.95)]
  • PK data show a large reduction in measurable nerinetide in the alteplase group
• **Neuroprotection in humans is possible.** This will be explored in further studies of nerinetide
Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): a multicentre, double-blind, randomised controlled trial