Independent Data Monitoring Committee (IDMC) Charter

REDACTED (Name of IDMC Members removed)

Study Name:
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

Protocol Number: NA-1-007 ESCAPE-NA1 Trial

Date: 3 March 2017  Version: Version 1.0
**Revision History**

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<th>Changes</th>
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1.0 Introduction

An Independent Data Monitoring Committee (IDMC) will perform periodic safety reviews of the clinical data for the clinical trial NA-1-007 (ESCAPE-NA-1). The reviews will occur when 100 and 600 subjects have reached their Day 90 final study visit and additional reviews may be completed as requested by the IDMC.

An efficacy interim analysis after approximately 600 subjects complete the Day 90 follow-up (~56% information) will be conducted using an alpha spending function\(^1\) with O’Brien- Fleming\(^2\) type stopping boundary for efficacy and a non-binding conditional power boundary (conditional power = 0.065%) for futility. For an interim analysis conducted at exactly 56% information, the superiority critical p-value for stopping (boundary value) would be 0.003 and that at the end of the study (primary analysis) would be 0.024, 1-sided. The IDMC may recommend stopping for overwhelming efficacy or for futility at the interim analysis if the test statistic crosses the O-F or conditional power boundary. The trial steering committee and the Sponsor will consider the IDMC recommendations in the context of the overall NA-1 development program, including possible input from regulatory agencies as it may relate to the IDMC recommendations.

This Charter is for the Independent Data Monitoring Committee (IDMC) for NA1-007 (ESCAPE-NA-1) Clinical trial with the Sponsor NoNO Inc. and the Coordinating Center the University of Calgary. The study has the following identification numbers:

- Clinicaltrials.gov: NCT02930018
- Health Canada File Number: HC6-24-c102145
- US FDA IND: 118,087
- EudraCT Number: 2016-001826-33

This Charter describes the roles and responsibilities of the IDMC and outlines the plan for the review of study data.
### 2.0 Study Description and Study Design

A full study synopsis can be found in Section 10.0, Appendix 2.

<table>
<thead>
<tr>
<th>Study name:</th>
<th>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</th>
</tr>
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<tbody>
<tr>
<td>Study design:</td>
<td>Phase 3, randomized, multicentre, blinded, placebo-controlled, parallel group, single-dose design. Subjects harboring an acute ischemic stroke and who are selected for endovascular revascularization in accordance with local institutional practices and who harbor a small established infarct core and with good collateral circulation will be given a single, 2.6 mg/kg intravenous dose of NA-1 or placebo as soon as they are deemed to have met the enrollment criteria and started within 30 minutes of randomization. The randomization will be by stochastic minimization to balance baseline factors.</td>
</tr>
<tr>
<td>Investigational drug:</td>
<td>Single, 2.6 mg/kg intravenous dose of NA-1 or placebo</td>
</tr>
<tr>
<td>Phase:</td>
<td>3</td>
</tr>
<tr>
<td>Number of planned patients:</td>
<td>1120</td>
</tr>
<tr>
<td>Number of planned sites:</td>
<td>35</td>
</tr>
<tr>
<td>Countries planned to participate:</td>
<td>Canada, USA, Ireland, United Kingdom, Sweden, South Korea, Australia</td>
</tr>
</tbody>
</table>
| Timeline Estimates | Estimated first patient enrolled: 6 February 2017  
Estimated 100th patient enrolled: 15 June 2017 + 90 days = 15 Sept 17  
Estimated 600th patient enrolled: 15 June 2018 + 90 days= 15 Sept 18  
Estimated 1120th patient enrolled: 30 June 2019  
Estimated last patient last visit: 30 Aug 2019 |
3.0 IDMC

3.1 Roles and Responsibilities

The IDMC is responsible for the review of study safety data on an ongoing basis and the evaluation of efficacy after 600 patients have completed Day 90. This IDMC will be independent of the Sponsor, the independent Statistical Group, Coordinating or Principal Investigator(s), site Investigator or site Sub-Investigator and Steering Committee membership or any other capacity related to study operations. Firewalls will be in place at the Statistical Group preparing all interim reports to protect and sequester all interim results on safety and efficacy. The IDMC will report to the trial Steering Committee.

The IDMC will:

- Review the study protocol and NA-1’s Investigator Brochure
- Attend the IDMC Initial Meeting and ratify the Charter
- Monitor the conduct of the study
- Review rates of recruitment, major protocol deviations and dropouts
- Review the overall data collection methods and safety monitoring procedures and make recommendations for additions or adjustments
- Review safety data and related parameters to be monitored, and make recommendations to the Steering Committee concerning continuation of the study, termination, continuation with modifications or requests for other data or analyses
- Maintain meeting records

The IDMC will review the safety results from Protocol No. NA-1-007, evaluate the treatment for adverse events (AE), and report to and make recommendations to the Steering Committee. The IDMC members will review the study data and make decisions about the continuation of the trial or suspension of the clinical study.

3.2 Selection of IDMC Members

The IDMC Chair and other members were selected by the Steering Committee based on their expertise with subjects with acute cerebral ischemia, and experience with other IDMCs and clinical trials in acute stroke. In the event that a member is unable to continue participation, the IDMC Chair will recommend a replacement to the Steering Committee.

3.3 IDMC Committee Composition

The Committee will consist of a Stroke Neurologist(s), Stroke Neuro-Interventionist(s) supported by an independent statistician. The duration of the membership for the IDMC will be inclusive of planned analyses for the study. The members are independent of the trial (i.e., not involved with the trial in any other way and do not have any scientific or financial competing interest that could impact on the trial). Financial Disclosure statements are declared in Appendix 3: Financial Disclosure Form.

The members of the IDMC are (redacted):

- Chair and Neuroradiologist: MD, Neuroradiologist
Statistician: Ph.D. Associate Professor

Neuroradiology: MD, Neuroradiology

Stroke Neurologist: MD, Professor, Department of Neurology
4.0 Roles and Responsibilities

4.1 Responsibilities of the Sponsor

With the support of the Coordinating Investigator, the Sponsor is responsible to:

- Obtain approval to conduct the study from each of the applicable health authorities for each of the countries participating in the trial.
- Provide the study Protocol and Investigator Brochure
- Provide medical expertise and scientific oversight
- Provide clinical management, oversee data monitoring, ensure compliance with the protocol and applicable regulations, maintain quality assurance and quality control including the conduct of audits
- Chemistry, Manufacturing and Controls (CMC); study drug manufacturing, packaging, labeling and coding per Good Manufacturing Practices (GMP), infusion pump and study drug administration kit shipment to EMS hubs
- Provide the clinical study report
- Maintain essential documents
- Communicate external evidence (e.g. safety data from other related trials)
- Communicate all pertinent regulatory information to the regulatory agencies and Investigators
- Notify the Investigators and regulatory agencies if the IND is withdrawn.

4.2 Responsibilities of the Co-ordinating Investigator

The Co-ordinating Investigator will be responsible to:

- Generate and manage the study protocol, through the Steering committee
- Along with the Sponsor, engage and contract with sites to conduct the study protocol
- Provide medical oversight for the study to ensure its accurate and careful completion
- Participate as part of the steering committee to manage the safety events within the trial, reporting to the Sponsor
- Along with the Sponsor, engage and contract, oversee and manage the data management group
- Contribute to the final study report

4.3 Responsibilities of the Clinical Study Monitors

The Clinical Study Monitors will be responsible to:

- Monitor individual case histories
- Assess adherence to the protocol
- Monitor of electronic case report forms (e-CRF) and source documents
- Ensure completeness and accuracy of all data entered into the e-CRF, including serious adverse event (SAE) information, to the extent required by the IDMC and the Steering Committee
- Assess adherence to Good Clinical Practice
4.4 Responsibilities of the Data Management Group

The Data Management Group will be responsible to:

- Ensure completeness of all data entered into the e-CRF, including SAE information, to the extent required by the IDMC and the Steering Committee
- Provide data sets to the statistical group containing all e-CRF data necessary for creating IDMC reports

4.5 Responsibilities of the Statistical Group

The independent Statistical Group will produce the IDMC Reports as well as the interim analysis of efficacy and provide them to the IDMC members. The IDMC Report will be provided one week prior to the meeting. The group will be unblinded and sequestered from the Project Team, steering committee and investigators.

The Statistical Group is responsible to:

- Prepare Tables, Figures and Listings for the IDMC to review
- Apply the treatment codes to the data to produce the unblinded reports by treatment group
- Perform a quality check of the results
- Forward the agreed-upon Tables, Figures and Listings to the IDMC

The IDMC Project Administrator, also a member of the Statistical Group (unblinded), will handle most communication between the IDMC and the Project Team, including the forwarding of the unblinded reports to the IDMC members and preparation of the Open and Closed Session meeting minutes. The IDMC Independent Reporting Statistician, also a member of the Statistical Group, also attends the Open and Closed Sessions of the IDMC meetings and answers any questions from the IDMC regarding the reports.

In contrast, the Project Statistician is on the blinded Project Team and will not produce, review or have access to unblinded aggregate reports for the IDMC during the study. The Project Statistician’s group will produce the Final Study Report after final database lock and unblinding of the trial.

4.6 Steering Committee

The Steering Committee is responsible for:

- Designing the study (and amending it as necessary)
- Maintaining the quality of the study conduct
- Monitoring of blinded safety data on an ongoing basis
- Writing the study publication
The Steering Committee consists of the following:

Michael D Hill, M.D.  
Coordinating Investigator  
Director of Calgary Stroke Unit  
University of Calgary  
Stroke Clinical Trial Group  

Karla Ryckborst, RN  
Global Study Nurse Coordinator  
Stroke Clinical Trial Group  

Mayank Goyal, M.D.  
Director of Stroke Imaging  
University of Calgary  
Stroke Clinical Trial Group  

Andrew M Demchuk, M.D.  
Director of Calgary Stroke Program  
University of Calgary  
Stroke Clinical Trial Group  

Bijoy K Menon, M.D.  
University of Calgary  
Stroke Clinical Trial Group  

Michael Tymianski, MD., Ph.D.  
President and CEO, NoNO Inc.  
Sponsor  

Ana DiLuciano  
Safety Manager, NoNO Inc.  
Sponsor  

Davis Chau  
Senior Clinical Project Leader, NoNO Inc.  
Sponsor  

Kathy Heard, MSc (Sponsor Contact)  
Director Clinical Development,  
NoNO Inc.  
Krembil Research Institute  
8KD-406, 60 Leonard Ave,  
Toronto, Ontario  
Phone: 1 647-924-3399  
Email: kheard@nonoinc.ca
5.0 Meetings

5.1 Initial Meeting

IDMC members will be provided with the protocol, Investigator Brochure, IDMC Charter and IDMC/Interim Analysis Plan for the study. IDMC members will be informed of any protocol amendments. The Initial Meeting will have the following objectives:

- Provide introductions
- Review of NA-1
- Review of NA-1’s nonclinical pharmacology and toxicology data
- Review of NA-1’s clinical data (safety and efficacy)
- Rationale for investigating NA-1 in subjects at a target dose of 2.60 mg/kg IV infusion
- Review of Protocol No. NA-1-007
- Provide a project update
- Review the Charter
- Review IDMC planned tables, listings and figures (Analysis Plan)

This meeting will allow the IDMC members to discuss the logistical issues pertaining to the IDMC such as content of the data reviews and the proposed meeting format and content of meetings. Competing interests and potential conflicts of interest will also be discussed. Sponsor (NoNO Inc.) representative(s) will participate in this meeting.

IDMC members will formally register their assent by confirming (1) that they agree to be on the IDMC and (2) that they agree with the contents of this Charter by providing their signature on Error! Reference source not found..

5.2 Meeting Schedule

The IDMC will convene for:

- An Initial Meeting prior to the first subject being randomized.
- Safety review meeting after the first 100 patients have completed reached their Day 90 final study visit.
- Interim analysis including safety and efficacy after 600 patients have completed their Day 90 visit.
- Additional periodic safety reviews of the clinical data (approximately every six months depending on enrolment rates), as deemed necessary by the IDMC and Steering Committee
- Final end of study meeting at the conclusion of the study

In the event of unforeseen circumstances, such as unexpected SAEs, etc., the Steering Committee or the IDMC Chair may request an unscheduled meeting.

5.3 Meeting Format (Open and Closed Sessions)

The Safety Data Review Meetings will be conducted in three consecutive sessions:

- An Open Session for a project update and review of administrative aspects of the study. This session will include the Steering Committee.
• A Closed Session for discussion of unblinded safety and efficacy results (as needed) and to develop a recommendation for the Steering Committee. This session will exclude the Steering Committee, Project Team members and anyone other than the unblinded IDMC members and the unblinded statistical group supporting the IDMC (preparing the unblinded reports by treatment arm).

• A Wrap-up Session to discuss the recommendations for the conduct of the study. This session will include the Steering Committee.

During the Open Session, the Steering Committee or delegate will make brief presentations to the IDMC regarding the study conduct and progress.

6.0 Data Review

6.1 Safety Review

The Safety reviews conducted when 100 and 600 patients have completed Day 90 visit will include:

• Cumulative summary statistics on enrollment
• Subject status in the study (e.g., number completed Day 90 visits), by treatment group
• Baseline characteristics, by treatment group
• Safety data, including AEs and SAEs by AE code, severity, and relatedness to the study medication, by treatment group
• Discontinuations due to AEs, by treatment group
• Comment on the balance of NA-1: placebo patients, demographics and other data quality and timing metrics during the trial.
• SAE Narratives
• Major protocol deviation-violations

6.2 Efficacy Review

The Efficacy review conducted when 600 patients have completed Day 90 visit will include:

• Day 90 mRS
• Results will be presented in overall summary by treatment group and also stratified by: (1) intravenous alteplase (tPA) treatment and (2) time from stroke onset (0-6h vs. 6-12h).

An efficacy interim analysis after approximately 600 subjects complete the Day 90 follow-up (~56% information) will be conducted using an alpha spending function with O’Brien- Fleming type stopping boundary for efficacy and a non-binding conditional power boundary (conditional power = 0.065%) for futility. For an interim analysis conducted at exactly 56% information, the superiority critical p-value for stopping (boundary value) would be 0.003 and that at the end of the study (primary analysis) would be 0.024, 1-sided.

The IDMC may recommend stopping for overwhelming efficacy or for futility at the interim analysis if the test statistic crosses the O-F or conditional power boundary.
6.3 Confidentiality of Data and Analyses

To ensure minimization of operational bias and confidentiality of the data, the data for the IDMC reports will be provided by the independent Statistical Group. This group is independent of the Sponsor and Project Team and will maintain firewalls between the unblinded safety data and personnel in the independent Statistical Group on one side (unblinded) and the Sponsor and Project Team on the other (blinded). No aggregate unblinded data reports will be seen or discussed by or with the blinded team during the trial, unless by documented exception to this Charter.

Data will be presented with the groups will be semi-unblinded and labelled Group A and Group B.

7.0 Reporting

7.1 Procedures for Recommendations

Duly voted and passed IDMC recommendations to the Steering Committee will be included in the minutes within one week of the meeting. Recommendations will also be transmitted verbally to the Steering Committee during the Wrap-up Session.

7.2 IDMC Reports

IDMC Reports will be described in the IDMC and Interim Statistical Analysis Plan and include the items described in above in Sections 6.1 and 6.2 above.

7.3 How Decisions or Recommendations Will Be Reached

The role of the Chair is to summarize discussions and encourage consensus; it may be best for the Chair to give their own opinion last.

It is recommended that every effort be made for the IDMC to reach a unanimous decision. If the IDMC cannot achieve this, a recommendation may pass with the majority of votes, provided that all members find the recommendation acceptable. Details of the vote should not be routinely included in the report to the Steering Committee.

Approaches for stopping the study for a safety concern will be discussed at the first IDMC orientation meeting. The balance of primary risks and benefits, the internal consistency of results, the consistency with, and nature of, external evidence, and the likelihood that the results would affect clinical practice will be considered. It is important that the implications (e.g., ethical, statistical, and practical) for the trial be considered before any recommendation is made.
Effort should be made for all members to attend a meeting. The Steering Committee will try to ensure that a date is chosen to enable this. If any IDMC members cannot attend at all, then the IDMC meeting will be re-convened at a time when all members can attend.

7.4 Recommendations and Stopping Rules

To prevent operational bias all interim results on safety and efficacy will be reported only to the IDMC, keeping the Sponsor, Project Team, investigators and subjects blind to results by treatment assignment during the study. Firewalls will be in place at the Statistical Group preparing all interim reports to protect and sequester all interim results on safety and efficacy, details reside with the Statistical Group.

The IDMC will take into consideration the following specific questions/issues at the time of interim analysis:

- If the O’Brien Fleming boundary for efficacy are crossed at interim analysis (see boundary details in Section 6.2 above and in the SAP) the committee will then consider that there is statistical evidence for overwhelming efficacy on the primary endpoint. The committee should judge if the boundary is crossed with a large enough threshold to be confident of the results and warrant a recommendation to stop early, based upon the absolute effect size, consistency of key secondary analyses, safety signals and in the context of the status of the knowledge in the field.

- The committee should then consider the primary outcome analysis using the ordinal logistic regression (proportional odds model). See Section 10 of the SAP.

- The committee is then entrusted with a decision to make recommendations about the continuation of the trial in the context of the data and the context of the current and known evidence about endovascular stroke treatment using their best judgment.

The IDMC Chair will complete the Outcome Form for reporting the results of the IDMC meetings to the Steering Committee this can be found in Appendix 2: IDMC Outcome Form.

7.5 Meeting Minutes

Minutes of the Open and Closed Sessions will be prepared by the IDMC Chairperson (or Project Administrator), distributed in a timely manner after each meeting, and reviewed and approved at the subsequent meeting or previously via email.

Minutes from the Open Session need not be extremely detailed but should include sufficient information to explain the rationale for any recommended changes. They will be forwarded to all attendees of the meeting, including the Steering Committee. Minutes of the Closed Session will only be reviewed and approved by the IDMC and the members of the independent statistical team preparing the reports. After final database lock, the minutes of the Closed Sessions will be forwarded to the Steering Committee.

An IDMC Outcome Form will be used for reporting the results of the IDMC meetings to the Steering Committee. The IDMC Chair will sign off the completed IDMC Outcome Form. The
signed Outcome Form should be e-mailed to the Steering Committee contact person within one week of the IDMC meeting. This IDMC Outcome Form may be shared with Principle Investigators.

7.6 Publications of Results

At the end of the trial there may be a meeting to allow the IDMC to discuss the final data with the Steering Committee and principal investigators and give advice about data interpretation.

IDMC members will be named and their affiliations listed in the final report, unless they explicitly request otherwise. They will not be considered authors for the final manuscript.

7.7 Steering Committee’s Response to IDMC Recommendations and Findings

The Steering Committee members will review and respond to the IDMC recommendations. If the IDMC recommends continuation of the study without modification, no formal response will be required. However, if the recommendations request action, such as a recommendation for termination of the study or modification of the clinical study protocol, the Steering Committee will provide a written response stating whether the recommendations will be followed and the plan for addressing the issues.

If major implications of the IDMC recommendation are questionable to the Steering Committee, the Sponsor may want to consult further with the IDMC or with regulatory agencies or other consultants before finalizing the response to the IDMC.

Upon receipt, the IDMC will consider the Steering Committee response and will make attempts to resolve relevant issues, resulting in a final decision for the IDMC recommendation. Appropriate caution will be necessary during this process to avoid compromising study integrity or the ability of the Steering Committee to manage the study, should the study continue. Specifically, all Sponsor employees, steering committee members and investigators will remain blinded to treatment codes and interim study results on safety and efficacy by treatment arm throughout the study. No aggregate unblinded data reports of safety or efficacy by treatment arm will be seen or discussed by or with the blinded team during the process of reviewing IDMC recommendations.

The Steering Committee will disseminate IDMC recommendations which result in actions and the Sponsor decision to the appropriate regulatory agencies, IRB/EC and Investigators within an appropriate time (usually with the amendment of the clinical study protocol).

In the unlikely event of irreconcilable differences between Steering Committee and IDMC, especially regarding study termination or other substantial study modifications, the IDMC may decide to discontinue monitoring the current study and disband. This decision will be communicated to the Steering Committee in writing.

Public disclosure of the IDMC recommendations/findings as well as the Steering Committee’s final decision will be at the discretion of the Steering Committee. The IDMC shall remain bound by confidentiality and will not make any public announcements either as a group or individually.
8.0 Additional Items

8.1 Payments to IDMC Members

IDMC Members will be reimbursed for preparation and attendance at all meetings, and for reasonable travel and accommodation for attendance at face-to-face meetings, if applicable. Otherwise, the IDMC members will be independent of the Steering Committee and not serve as paid consultants regarding NA-1-007 clinical trial or the investigational product or in other ways entertain competing interests; financial or scientific. Payments to the DSMB will be in the form or an honourarium.

8.2 Competing Interests

IDMC Members may not participate in the study as part of the Steering Committee, Investigators, or as study patient care physicians. Members of the IDMC will not buy, sell, or hold stock or stock options from the Sponsor (NoNO Inc.) until the final IDMC meeting or until the member’s active personal involvement in the IDMC ends. Each IDMC member will complete a Financial Disclosure form found in Appendix 3: Financial Disclosure Form.

Certain other activities are not viewed as constituting conflicts of interest, but must be reported to the IDMC Chairperson. These include: Participation of members in other research projects supported by the Sponsor and occasional scientific consulting to the Sponsor on issues not related to the product in the trial.

8.3 Blinding

The IDMC will be semi-unblinded as to the treatment (NA-1 or placebo) received by each subject for the safety review. The IDMC will be semi-unblinded for the interim analysis after 600 patients for both efficacy and safety. The IDMC will have access to full unblinding at any time during their review at all review meetings. The IDMC will have access to the treatment information at all times for their reviews.

8.4 External Evidence

Identification and circulation of external evidence (e.g. safety data from other related trials) to the IDMC will be the responsibility of the Steering Committee.

8.5 Confidentiality

All members of the IDMC will treat as confidential the Safety Reports, meeting discussion and minutes, and agree that all material, documents and information provided to them and all information developed by the IDMC shall be considered as confidential information and the sole property of the Sponsor. Confidentiality shall be governed by the Agreements between Sponsor and each of the respective Parties.

8.6 Amendments to the IDMC Charter
This IDMC Charter can be amended as needed during the course of the study. Information to be included as amendments will be any modifications or supplements to the reports prepared for the IDMC, as well as amendments to other information addressed in this Charter. All amendments will be documented with sequential version numbers and revision dates, and will be recorded in the minutes of the IDMC meetings. Each revision will be reviewed and agreed upon by the IDMC chairperson and the Steering Committee. All versions of the Charter will be archived in the Trial Master File.

8.7 IDMC Closeout

The Sponsor will provide relevant sections of the clinical study report for acknowledgement or review by the IDMC. The IDMC may recommend continuing action items to the Sponsor based upon the final review. The IDMC may be invited by the Sponsor to the end of study meeting, if applicable for presentation of analyzed data arising from the study.

9.0 References


### 10.0 Appendices

#### Appendix 1: Study Synopsis

<table>
<thead>
<tr>
<th><strong>Trial Objectives</strong></th>
<th>The primary objective is to determine the efficacy of the neuroprotectant, NA-1, in reducing global disability in subjects with major acute ischemic stroke (AIS) with a small established infarct core and with good collateral circulation selected for rapid endovascular revascularization. The secondary objectives are to determine the efficacy of NA-1 in:</th>
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<tr>
<td></td>
<td>• Reducing functional dependence</td>
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<tr>
<td></td>
<td>• Improving neurological outcome</td>
</tr>
<tr>
<td></td>
<td>• Improving activities of daily living</td>
</tr>
<tr>
<td></td>
<td>• Reducing mortality rate</td>
</tr>
<tr>
<td><strong>Trial Design</strong></td>
<td>This study is a Phase 3, randomized, multicentre, blinded, placebo-controlled, parallel group, single-dose design. Subjects harboring an acute ischemic stroke and who are selected for endovascular revascularization in accordance with local institutional practices and who harbor a small established infarct core and with good collateral circulation will be given a single, 2.6 mg/kg intravenous dose of NA-1 or placebo as soon as they are deemed to have met the enrollment criteria and started within 30 minutes of randomization. The randomization will be by stochastic minimization to balance baseline factors.</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>Up to 1120 male and female subject will be enrolled. 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 National Institutes of Health Stroke Score (NIHSS) &gt; 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) &gt; 90 (95 or 100). Patient must be living in their own home, apartment or seniors lodge where no nursing care is required. 6) Confirmed symptomatic intracranial occlusion, based on multiphase or dynamic computerized tomographic angiography (CTA), at one</td>
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or more of the following locations: Intracranial carotid T/L, M1 middle cerebral artery (MCA). Functionally, when defining the M1 or the M2, the bulk of the MCA territory must be ischemic.

7) Non-contrast computed tomography (NCCT) and CTA* for trial eligibility performed or repeated at ESCAPE-NA1 stroke centre with endovascular suite on-site.

8) Endovascular treatment with declared first endovascular approach as either stent retriever or aspiration device, and intended to be initiated (arterial access) within 60 minutes of baseline/qualifying NCCT and to first recanalization of 90 minutes. Study drug intended to be administered within 60 minutes of the baseline/qualifying NCCT.

9) Signed informed consent from subject or legally authorized representative.

*As per the List of Abbreviations (Section Error! Reference source not found.), all references to CTA indicate a multiphase or dynamic CTA.

Exclusion Criteria

1) Evidence of a large core of established infarction defined as ASPECTS 0-4.

2) Evidence of absence of collateral circulation on CTA (Collateral score of 0 or 1).

3) Intent to use any endovascular device other than a stent retriever or clot aspiration device or intra-arterial medications as the initial thrombectomy approach.

4) Intent to use any intravenous thrombolytic other than alteplase if intravenous thrombolysis is planned.

5) No femoral pulses, very difficult endovascular access or extreme tortuosity of great vessels that is predicted to result in an inability to deliver timely endovascular therapy. Direct common carotid or radial/brachial/axillary access is permissible.

6) Estimated or known weight > 120 kg or < 45 kg.

7) Pregnancy; if a woman is of childbearing potential a urine or serum beta human chorionic gonadotropin (β-hCG) test is positive, or breastfeeding.

8) Severe contrast allergy or absolute contraindication to iodinated contrast preventing endovascular intervention.

9) Clinical history, past imaging or clinical judgment suggests that the intracranial occlusion is chronic or there is suspected intracranial dissection such that there is a predicted lack of success with endovascular intervention.

10) Prior enrolment in the ESCAPE-NA1 trial or prior receipt of NA-1 for any reason.
11) Severe known renal impairment defined as requiring dialysis (hemodialysis or peritoneal) or if known a creatinine clearance < 29 mL/min.
12) Patient has a severe or fatal comorbid illness that will prevent improvement or follow-up.
13) Patient cannot complete follow-up treatment due to co-morbid non-fatal illness or they are known to be a visitor to the city or any other known reason for which follow-up would be impossible (e.g. incarcerated in a federal prison).
14) Participation in another clinical trial investigating a drug, medical device, or a medical procedure in the 30 days preceding study inclusion.

<table>
<thead>
<tr>
<th>Countries</th>
<th>Canada, U.S., Ireland, Sweden, South Korea, United Kingdom, Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>NA-1 2.6 mg/kg (or matching normal saline placebo volume) will be administered as a single 10 ± 1 minute intravenous infusion 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. Stent retrievers or aspiration devices will be used according to current local jurisdictional guidelines.</td>
</tr>
<tr>
<td>Consent</td>
<td>Explicit written, signed informed consent from the subject or legally authorized representative (LAR) will be obtained prior to any protocol-specific procedures. If the original consent was obtained from the LAR and if required by local standards, consent will be sought for the remaining procedures from the subject once they are deemed to have regained capacity.</td>
</tr>
<tr>
<td>Duration of Treatment</td>
<td>This study consists of one 90-day study period for each subject. Subjects will be hospitalized for care after their acute stroke according to the current standard of care. Subjects are required to return to clinic on Days 30 and 90 for end-of-study procedures.</td>
</tr>
<tr>
<td>Laboratory Tests</td>
<td>In order to support the assessment of patient safety baseline (pre-dose) and post dose hematology, chemistry laboratory tests will be completed. At baseline, and at 24 ± 12 hours after study drug infusion and termination of EVT, blood work will be evaluated which includes: complete blood count (CBC), electrolytes, international normalized ratio (INR), activated prothrombin time (aPTT), serum creatinine and serum glucose. Other laboratory or point-of-care testing may be performed at the discretion of the attending physicians and team.</td>
</tr>
</tbody>
</table>
If the subject is female and is of childbearing potential, a pregnancy test (urine or serum point-of-care pregnancy test) must be completed and a negative test result obtained prior to inclusion in the trial.

Electrocardiograms will also be collected and reviewed at baseline (pre-dose, unless impeding access to timely intervention) and at 24 hours.

**Assessment of Efficacy and Power**

The primary efficacy outcome variable for the pivotal assessment of efficacy for regulatory submission purposes is the overall proportion of subjects experiencing a favorable functional outcome 90 days post-randomization, defined as a score of 0 to 2 on the modified Rankin Scale (mRS). These subjects are defined to be responders. Assuming a 52% overall responder rate for the placebo group, there will be an estimated 80% power to detect an 8.7% absolute effect difference between response rate (proportion of responders, with Day 90 mRS in the range 0 to 2) with NA-1 and placebo, at alpha level 0.025, 1-sided with a planned sample size of 1076 evaluable subjects, randomized 1:1, per group, accounting for a single interim analysis when 600 subjects have completed their 90 day follow up visit information (600 subjects with primary endpoint assessments) with O’Brien-Fleming alpha-spending function stopping boundary for overwhelming efficacy and a non-binding 1% conditional power futility stopping boundary (EaST® V6.3). The sample size will be inflated approximately 4% to N=560 per group to account for loss-to-follow-up and drop-outs.

The primary hypothesis to be tested is that administration of NA-1 will result in an increase in the proportion of subjects with independent functioning on the mRS (as defined by a score of 0-2) at Day 90. The primary analysis will be a Wald test for treatment group difference in the primary outcome from a logistic regression including treatment and the following important prognostic factors: intravenous alteplase treatment, intended initial endovascular approach as well as age, baseline NIHSS score and site.

The primary efficacy analysis and secondary endpoint analyses will be conducted on the intent-to-treat (ITT) population, defined as all subjects randomized into the trial with grouping by randomized treatment, regardless of treatment actually received. Deceased subjects will be included in the ITT population with a mRS score of 6.

A key secondary outcome analysis is planned to evaluate a shift of one or more categories to reduced functional dependence analyzed across the whole distribution of scores on the mRS at Day 90 or the last rating. This secondary outcome will be an adjusted analysis using a proportional odds model to derive the common odds of improvement (“shift”) along the mRS scale. Adjustment will include all of the variables used in stratification (intravenous alteplase treatment, intended initial endovascular approach) and in the minimization
algorithm (age, baseline NIHSS score, baseline ASPECTS score, occlusion location, and site). The proportional odds assumption will be tested using a Brant test.

Other secondary outcomes include:

1) 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.
2) Proportion of subjects with functional independence in activities of daily living, as defined by a score of ≥ 95 on the BI at Day 90 or the last rating.
3) A reduction in mortality rate, as defined by event rate (%) for mortality over the 90 day study period
4) Proportion of subjects with functional independence, as defined by a score of 0-1 on the mRS at Day 90 or the last rating.

<table>
<thead>
<tr>
<th>Assessment of Safety</th>
<th>For the safety analysis, the frequency of SAEs, 90-day mortality, adverse events (AEs), discontinuations due to AEs. As well, baseline and post-dose study drug vital signs, laboratory (hematology and chemistry) and electrocardiogram (ECG) findings will be analyzed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent Data Monitoring Committee</td>
<td>An Independent Data Monitoring Committee (IDMC) will perform periodic safety reviews of the clinical data. The reviews will occur once 100 and 600 subjects have reached their Day 90 final study visit. An efficacy interim analysis (after approximately 600 subjects complete the Day 90 follow-up) will be conducted using the alpha spending function method(^1) with O’Brien and Fleming(^2) type stopping boundary for efficacy and a non-binding conditional power boundary for futility. The trial may be stopped for overwhelming efficacy or futility at the interim analysis if the test statistic crosses the O’Brien-Fleming (O-F) or conditional power boundary.</td>
</tr>
<tr>
<td>Bioanalytical Method</td>
<td>The plasma concentrations (immunogenicity) of NA-1 from a subset of up to 250 subjects from sites located in Canada will be analyzed using a validated direct ELISA assay method. Pharmacokinetic assessments from a subject of up to 100 subjects from a subset of sites located in Canada will be evaluated.</td>
</tr>
</tbody>
</table>
Appendix 2: IDMC Outcome Forms

NA-1-007 ESCAPE-NA-1 Clinical Trial - IDMC Data Review#1 Outcome Form

From: NAME (Chair)

To: NoNO Inc, c/o Kathy Heard

The IDMC conducted their review on the data for the first 100 patients on dd MMM yyyy.

Based on the review, the IDMC recommends:

___1. The study may continue without modification
___2. The study may continue with modifications (See Comments)
___3. The study should be discontinued for a safety concern (See Comments)
___4. More data are required (See Comments)

Comments:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Signature: ___________________________ Date: ___________________________


NA-1-007 ESCAPE-NA-1 Clinical Trial - IDMC Data Review #2 (Interim Analysis) Outcome Form

From: NAME (Chair)

To: NoNO Inc, c/o Kathy Heard

The IDMC conducted their review on the data for the first 600 patients on dd MMM yyyy. Based on the review, the IDMC recommends:

1. The study may continue without modification
2. The study may continue with modifications (See Comments)
3. The study should be discontinued for a safety concern (See Comments)
4. More data are required (See Comments)
5. The study should be stopped due to overwhelming efficacy
6. The study should be stopped due to futility

Comments:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

Signature: ___________________________ Date: __________________________
Appendix 3: Financial Disclosure Form

Financial Disclosure Form

Please complete both pages of this form prior to participation in the study. If your spouse or dependent children have new financial interests or arrangements (i.e., an answer changes from No to Yes) during the study, a new Financial Disclosure Form needs to be completed.

1. **Protocol Title:** A Multicentre, Randomized, Double-blind, 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)

2. **Drug Name/Number:** NA-1

3. **Study Number:** NA-1-007

4. **Site Number:** NA: IDMC member

5. **IDMC Member Name:**

6. **Institution Name (if applicable):**

7. **Address:**

Check YES or NO if any of the financial interests or arrangements described below apply to you, your spouse, or dependent children

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
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<tbody>
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</table>

- Financial arrangements with NoNO Inc. whereby the value of the compensation could be influenced by the outcome of the Study.
  - If YES, please disclose details:

- Proprietary interest (i.e., any property or other financial interest, including but not limited to, patents, trademarks, copyrights or licensing arrangements) in the tested product which is the subject of the Study.
  - If YES, please disclose details:

- Any equity interest in NoNO Inc. during the clinical Study and within one (1) year following completion of the Study. This would include
  - any equity interest that exceeds US $50,000 in value and/or
  - any ownership interest, stock options or other financial interest whose value cannot be readily determined through reference of public prices.
  - If YES, please disclose details:

- Significant payments of other sorts, which are payments that have a cumulative monetary value of US $25,000 or more made by NoNO Inc. during the clinical Study or within one (1) year following completion of the Study, excluding the costs of conducting the study or other clinical studies. This could include e.g., grants to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria.
  - If YES, please disclose details:
I undertake to promptly notify NoNO Inc. in writing if I, my spouse or dependent children have new financial interests and arrangements during the course of the Study or one year thereafter.

I undertake to provide NoNO Inc. with the “Financial Certification/ Disclosure Form – End of Study Verification” attached as Appendix hereto at the end of the Study (or earlier if I withdraw from study participation prior to end of the Study).

I declare that the information provided on this form is to the best of my knowledge and belief, true, correct, and complete.

Authorization for Access and Transfer of financial Data

I am aware that NoNO Inc. is entering my personal financial data into electronic internal databases. This concerns my personal financial data collected prior to, throughout and within one year following the completion of the Study, including – without limitation – my answers in this questionnaire and further financial data provided by myself.

NoNO Inc. may allow the following entities to access such data and may transfer such data to the following entities, as required, in accordance with applicable legal requirements:

Affiliated companies of NoNO Inc., ECs / IRBs and other third parties directly involved in the conduct of the Study (e.g. CROs), and/or other authorities.

NoNO Inc. will perform or have third parties perform the aforementioned entry, data processing, use and transfer in accordance with the applicable data protection laws.

I hereby authorize NoNO Inc. to store my personal financial data in data bases and process such data in accordance with applicable legal requirements. This concerns my personal data collected prior to, throughout and within one year following the completion of the Study, including – without limitation – my answers in this questionnaire and further financial data provided by myself.

In addition, I hereby authorize NoNO Inc. to grant access and transfer my personal financial data to the following entities, as required, in accordance with applicable legal requirements: Affiliated companies of NoNO Inc., ECs / IRBs and other third parties directly involved in the conduct of the Study (e.g. CROs), and/or other authorities.

I hereby authorize NoNO Inc. to perform or have third parties perform aforementioned entry, data processing, use and transfer.

Signature: Date:

Print Name:

Prior to study start, please return a copy of the signed form to Kathy Heard (kheard@nonoinc.ca) and retain the original of the form in your file.