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CLINICAL AND STATISTICAL ANALYSIS PLAN

PRODUCT UNDER INVESTIGATION:

Silk Road Medical, Inc.
NOVIS Transcarotid Neuroprotection System

FEASIBILITY STUDY OF THE TREATMENT OF ACUTE ISCHEMIC STROKE USING THE NOVIS TRANSCAROTID NEUROPROTECITON SYSTEM IN TRANSCAROTID EMBOLECTOMY:

THE NITE 1 STUDY

PROTOCOL NUMBER
SRM-2019-01

ANALYSIS SPONSOR
Silk Road Medical, Inc.
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PREPARED BY
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DATE AND VERSION
May 31, 2024 (Version 2.0)

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1. LIST OF ABBREVIATIONS

Abbreviations and Terms	Explanation
ACT	Activated Clotting Time
AIS	Acute Ischemic Stroke
CEA	Carotid Endarterectomy
CNI	Cranial Nerve Injury
DAPT	Dual Antiplatelet Therapy
ITT	Intention to Treat
LVO	Large Vessel Occlusion
MAE	Major Adverse Event
MI	Myocardial infarction
NPS	Neuroprotection System
PP	Per Protocol
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SICH	Symptomatic Intracranial Hemorrhage
TCAR	Transcarotid Artery Revascularization

2. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to prospectively outline the methods for analyses for patients with acute ischemic stroke in the anterior circulation due to large vessel occlusion (LVO) who underwent endovascular treatment using the transcarotid approach with flow reversal in this initial feasibility (NITE 1) study using the NOVIS Neuroprotection System (NPS).

The NITE 1 study is a prospective, multi-center, single arm feasibility study for the endovascular treatment of patients with acute ischemic anterior circulation strokes due to large vessel embolic occlusions using the transcarotid approach with flow reversal. Patients enrolled into the NITE 1 study will have failed transfemoral therapy and will be followed immediately from post-op to 90 days. The primary study objective is to establish the feasibility and safety of the NOVIS NPS in the targeted study population, and as such, this SAP will focus on confirming whether the initial safety signal exists from the primary endpoint data.

With FDA's IDE approval of the study design and sample size, the primary safety study endpoints will be numerically compared to existing TCAR data from the ENROUTE NPS clinical program (PROOF and ROADSTER). The functional independence at 90 days will be compared to reference data for acute ischemic stroke (AIS) patients treated with mechanical thrombectomy and the natural history of AIS in those patients who have not received or have failed mechanical thrombectomy, as cited in Section 5. The primary study endpoints for the NITE 1 study include:

- Device-related Serious Adverse Events – vascular complications including dissection, pseudoaneurysm, hematoma, arteriovenous fistula, thrombus formation, embolization and any vascular complication that may be attributed to the device AND requires surgical repair, surgical wound revision, transfusion, etc.
- Other Serious Adverse Events – permanent cranial nerve injury (CNI), new symptomatic intracranial hemorrhage (SICH) and dissections related to ancillary devices
- Functional independence at 90 days (proportion with mRS score 0-2)

Serious Adverse Events will be tabulated and reported accordingly. The primary endpoint and all secondary endpoints will be analyzed based on both the ITT and PP population. All available data on the ITT patients who were enrolled in the study will be included. This SAP presents the data results to be reviewed in evaluating the device-related SAEs, other SAEs, and functional independence at 90 days. Secondary endpoints to be summarized include the following:

- Carotid access time
    - Hospital arrival to neck incision
    - Neck incision to carotid exposure
    - Neck incision to carotid artery catheterization (includes securement of sheath)
    - Neck incision to femoral venous sheath access (includes securement of sheath)
    - Neck incision to initiation of reverse flow
- Time to final revascularization
    - Hospital arrival to OR
    - Last known well to final revascularization

  - Admission to final revascularization
  - OR to final revascularization
  - Cutdown to final revascularization
  - Arterial introduction of interventional tools to final revascularization
  - Total reverse flow time (CCA clamp to CCA unclamp)
- Device-related complications
- Neurologic assessment at 90 days (proportion of patients with a nondisabling or disabling stroke according to NIHSS)
- Technical success rate – Successful introduction of endovascular tools through the NOVIS Transcarotid NPS.
- Rates of revascularization success assessed by angiographic core lab (mTICI ≥ 2b)

To determine if the NOVIS NPS patients are comparable in safety to TCAR patients using the ENROUTE NPS, the following mutually exclusive populations will be compared:

Within the ***Complete NOVIS NPS Population***: All NOVIS NPS patients who were enrolled as part of the ITT study population in the NITE 1 study.

Within the ***Complete TCAR Population***: All TCAR patients who were enrolled in the ENROUTE clinical program (PROOF, and ROADSTER studies) and underwent the procedure.

There will be two independent sets of analyses performed to assess comparability between both patient populations – one using the ITT NITE 1 study population and the second using the Per Protocol NITE study population. The research questions, datasets, methods of analysis, and summarization of the results will be discussed in this SAP. The general design of the analysis summary tables, figures, and patient data listings used to present the analysis results are also presented in this plan.

The planned analyses identified in this SAP may be included in regulatory submissions, medical presentations and manuscripts. Exploratory analyses, not pre-identified in this SAP, may be performed to support the clinical development program.

3. OVERVIEW OF THE NOVIS TRANSCAROTID NPS SYSTEM

The Silk Road NOVIS Transcarotid NPS consists of four primary components:

- Transcarotid Arterial Sheath with Arterial Dilator
- Venous Return Sheath with Venous Dilator
- Flow Controller with Filter
- 0.035” Extra Support, J-Tip Guidewire

When assembled, the NOVIS Transcarotid NPS creates an arteriovenous shunt that can reverse the flow of blood in the carotid artery from antegrade to retrograde, shunting embolic particles away from the cerebral circulation during endovascular interventions. The NOVIS NPS is intended to provide vascular access and embolic protection during treatment with neurothrombectomy devices; it is not intended to aspirate the carotid artery and its branches or to perform mechanical neurothrombectomy at a distance from the site of occlusion. Device depictions and components are provided in the NITE 1 Clinical Protocol.

4. STATISTICAL RATIONALE FOR THE NITE 1 FEASIBILITY STUDY

The Intent-to-Treat (ITT) population is defined as enrolled patients who have consented, meet all inclusion and none of the exclusion criteria, and in whom transfemoral therapy has been deemed a failure. The per protocol (PP) population will be comprised of patients from the ITT population AND for whom no major protocol deviations have occurred. If the deviation meets any of the following criteria, it is considered a major protocol deviation:

- changing the protocol without prior IRB approval,
- failure to obtain informed consent, or
- falsifying research or medical records

The NITE 1 study protocol aims to recruit a minimum of 30 and a maximum of 40 patients in the PP population and to be analyzed in this study, unless the study enrollment is stopped sooner due to decision by the DSMB or Sponsor. Enrollment in the ITT cohort will cease when a targeted 30 PP patients have been accrued and complete the study follow-up period. Additional patients beyond 30 who are successfully enrolled while waiting for the 30th PP patient to complete the 90-day follow-up period, will be analyzed in the cohort for which they qualify, whether PP or ITT. Enrollment will continue till a maximum of 60 patients are enrolled in the ITT population or the study enrollment is stopped by decision from the DSMB or Sponsor.

Serious Adverse Events will be tabulated and reported accordingly. The primary endpoint and all secondary endpoints will be analyzed based on both the ITT and PP population. All available data on the ITT patients who enrolled in the study will be included.

5. REVIEW OF THE DATA RESULTS AND THE PROPOSED METHOD OF ANALYSIS

The data results have been broken down into 3 groups based on the primary endpoints outlined in the NITE 1 protocol, as listed below, and will be applied to both the ITT and PP population.

- Device-related Serious Adverse Events (SAEs) – vascular complications including dissection, pseudoaneurysm, hematoma, arteriovenous fistula, thrombus formation, embolization and any vascular complication that may be attributed to the device AND requires surgical repair, surgical wound revision, transfusion, etc.
- Other Serious Adverse Events – permanent CNI, new SICH and dissections related to ancillary devices.

- Functional independence measured at 90-day mRS (proportion with mRS score 0-2)

As listed above, the first data review will compare the incidence of the device-related SAEs from NITE 1 to the device-related SAEs collected across the body of TCAR evidence to date. This comparison group will include device-related SAEs from the ENROUTE NPS clinical program (e.g., PROOF and ROADSTER) representing a patient population spanning from feasibility to pivotal to post-market study settings. In addition, the incidence of permanent CNI and new SICH from the NITE 1 patient population will be compared to the same comparison group as well as reference data for AIS patients treated with mechanical thrombectomy and the natural history of AIS in those patients who have not received or have failed mechanical thrombectomy. The use of ENROUTE NPS clinical program data as a point of comparison for device-related SAEs and permanent CNI is based on the comparability of ENROUTE NPS and NOVIS NPS. Although each device is used for different patient populations, the surgical approach and set-up of each NPS device are equivalent. In regard to new symptomatic hemorrhage, the risk for this event can be attributed to two main causes: the risk due to cerebral reperfusion injury and the risk due to interventional or mechanical manipulation of the cerebral vasculature. The first applies to both ENROUTE NPS and NOVIS NPS, since any carotid revascularization comes with risk for cerebral reperfusion injury. The latter may be considered more specific to the AIS patient population. However, due to the increased risk for bleeding among patients treated with ENROUTE NPS due to required use of DAPT pre-procedure and systemic heparinization during the procedure to achieve an ACT of > 250, which is not applicable in the NOVIS NPS procedure for AIS patients, these risks can be considered to offset one another in each population. Therefore, the occurrence for SICH from ENROUTE NPS procedures can be compared to NOVIS NPS. Next, the incidence of dissections related to ancillary devices will be compared to the dissections related to the ancillary devices used commercially for ENROUTE and captured through post-market surveillance data. These numerical comparisons are summarized below with reference to the outcome, comparison group. Finally, the functional modified Rankin Score (mRS) at 90 days will be compared to the average functional independence score at 90 days (mRS 0-2) from the relevant studies included in the meta-analysis by Mokin M, et al in AIS patients treated with mechanical thrombectomy and the natural history of AIS in those patients who have not received or have failed mechanical thrombectomy. These data comparisons are summarized in Table 1 below:

Table 1. Summary of Planned Data Reviews for NITE 1

Outcome	**Comparison Group**
Device-related SAEs	Device-related SAEs from the ENROUTE NPS clinical program
Other SAEs: Permanent CNI	Permanent CNI from the ENROUTE NPS clinical program
Other SAEs: new symptomatic hemorrhage	New symptomatic hemorrhage from the ENROUTE NPS clinical program and from

	referenced literature in a similar patient population (e.g. San Román et al.[2])
Other SAEs: Dissections related to ancillary devices	Dissections from ENROUTE NPS clinical program
Functional independence at 90 days (proportion with mRS score 0-2)	Compared to the average mRS (0-2) score at 90 days from referenced literature in a similar patient population (e.g. Mokin et al.[1])

5.1. Handling of Missing Neuro Assessment Data at the Final Analysis

All efforts will be put forth to ensure near complete follow-up is obtained, in particular with the assessment of the primary outcome (mRS at 90 days). The final analysis will be conducted when all subjects have reached the upper limit of the window for the 90-day follow-up window (105 days after index procedure), and when the study sites believe they have exhausted all reasonable efforts to obtain outcome data collected within the window.

Nevertheless, some missing data may result. Missing 90-day mRS data (no mRS available within a 75-105 day window) will be handled by imputing the 30-Day mRS. In the case of patient death prior to the completion of the 90-Day visit, the subject will be counted as a failure (mRS = 6).

Missing 90-day NIHSS data (no NIHSS available within a 75–105-day window) will be handled by imputing the 30-Day NIHSS. In the case of missed 30-day NIHSS or of potential death prior to the completion of the 90-Day visit, the last study reported NIHSS will be imputed for analysis.

5.2. Imaging Analysis

Pre-operative and post-operative imaging will be evaluated by an independent imaging core lab, and interpretative findings will be reported in the final study report.

6. BASELINE DEMOGRAPHICS

6.1. Patient Accounting

A complete accounting of NITE 1 patients will be presented in Table 6.1 entitled *Patient Accounting (NITE 1 Population*). Listing 6.1 entitled *Patient Disposition* supports Table 6.1. This Listing will be sorted by patient number and will contain the reason for discontinuation (if applicable), along with the date of the last observation.

6.2. Baseline Demographic Factors

All patients in the NITE 1 population will be included in Table 6.2 entitled *Summary of Patient Demographics* (ITT Population). This table summarizes the patient population with respect to gender, age in years at the time of the procedure, race, and ethnicity. Age will be summarized

using descriptive statistics. The number and percent of each gender, race, and ethnicity category will be presented using counts and percentages. The supportive data for Table 6.2 will be presented in Listing 6.2 entitled *Patient Demographics*. This listing will be sorted by patient number.

6.3. Relevant Medical History

Results will be presented based on the reported medical history for the NITE 1 population. Results will be summarized and presented in Table 6.3 entitled *Summary of the Relevant Medical History and* Table 6.3.1 *Summary of Relevant Neurological History* . The patients will be summarized using counts and percentages for those patients who had a pre-index procedure medical history and neurological history. The supportive data for this table will be presented in Listing 6.3 entitled *Relevant Medical History* and Listing 6.3.1 *Relevant Neurological History.* This listing will be sorted by patient number.

7. PROCEDURE AND TREATMENT ADMINISTRATION

This section will describe the summarization and analysis of the administration of the treatment and the exact procedure.

7.1. Summary of Procedures and Treatments

Results will include descriptive statistics for the variable collected during the procedure based on the NITE 1 population. A summary of the results will be presented in Table 6.4 entitled *Summary of Procedures and Treatments* (ITT Population). Results will be supported by the data presented in Listing 6.4 *Procedures and Treatments*, sorted by patient number and the date of procedure.

7.2. Summary of Procedures Time Metrics

Procedural time related results will be tabulated and presented in Table 6.4.1 entitled *Summary of Procedural Time Metrics*. Continuous parameters will be summarized using descriptive statistics. Results will be supported by the data presented in Listing 6.4.1 *Procedural Time Metrics*, sorted by patient number and the date of procedure.

7.3. Summary of Technical Success

The Technical Success Rate is defined as successful introduction of endovascular tools through the NOVIS Transcarotid NPS. Results will be tabulated using counts and percentages and presented in Table 6.4.2 entitled *Summary of Technical Success*. Results will be supported by the data presented in Listing 6.4.2 *Technical Success*, sorted by patient number and the date of procedure.

7.4. Summary of Revascularization Success

Revascularization Success is defined as an mTICI of ≥ 2 as assessed by the angiographic core lab. Results will be tabulated using counts and percentages and presented in Table 6.4.3 entitled *Summary of Revascularization Success*. Results will be supported by the data presented in Listing 6.4.3 titled *Angiographic Core Lab Adjudication of Postprocedural mTICI*, sorted by patient number and the date of procedure.

8. SAFETY

Safety will be assessed by the Data Safety Monitoring Board and events will be adjudicated for review by the Clinical Events Committee, as outlined in the NITE 1 protocol. For final analysis of the safety events, binary rates will be calculated using a denominator as the number of all subjects in the study regardless of their follow-up time.

8.1. Adverse Events

The number and percentage of patients experiencing Adverse Events will be summarized. Summary Table 6.5 entitled Summary of Site-Reported Adverse Events by Event Type. Results will be supported by the data presented in Listing 6.5 *Adverse Events*, sorted by patient number and the date of procedure.

8.2. Serious Adverse Events

Summary Table 6.6 entitled Overall Summary of Serious Adverse Events will include counts and percentages. Results will be supported by the data presented in Listing 6.6 *Serious Adverse Events*, sorted by patient number and the date of procedure.

8.2.1.1. Summary of Device-Related Serious Adverse Events

All summaries of device-related SAEs will be presented separately and for the individual events.

The number and percentage of patients experiencing device-related SAEs will be summarized. Summary Table 6.6.1 entitled *Summary of Site-Reported Device-Related Serious Adverse Events* will include counts and percentages of patients (and event counts) following the category listed below. Results will be supported by the data presented in Listing 6.6 *Serious Adverse Events*, sorted by patient number and the date of procedure.

- vascular complications including dissection
- pseudoaneurysm
- hematoma
- arteriovenous fistula
- thrombus formation
- embolization
- any vascular complication that may be attributed to the device AND requires surgical repair, surgical wound revision, or transfusion

8.2.1.2. Summaries of Other SAEs

All summaries of other SAEs will be presented separately and for the individual events:

- Permanent CNI
- New SICH
- Dissections related to ancillary devices

The number and percentage of patients experiencing other SAEs will be summarized. Summary Table 6.6.2 entitled *Summary of Other Serious Adverse Events* will include counts and percentages of patients (and event counts) following the category listed above.

8.3. CEC Adjudicated Adverse Events

The number and percentage of events adjudicated by the CEC will be summarized. Summary Table 6.7 entitled Summary Adverse Events Adjudicated by the CEC. Listing 6.7 entitled CEC Adjudications supports Table 6.7.

9. NEUROLOGICAL EVALUATIONS

9.1.1.1. Summary of Functional Independence at 90 Days

The summary of functional independence at 90 days is defined as the proportion of NITE 1 patients with mRS score 0-2 at 90 days and will be presented in Table 6.8 entitled *Summary of Functional Independence at 90 days*. Listing 6.8 entitled *Modified Rankin Scale (mRS)* supports Table 6.8.

9.1.1.2. Summary of Neurologic Assessment at 90 days

The summary of neurological assessments at 90 days is defined as the proportion of NITE 1 patients with a nondisabling or disabling stroke according to the NIHSS and will be presented in Table 6.9 entitled *Summary of Neurological Assessment at 90 days*. An NIHSS of ≤ 4 is indicative of a nondisabling stroke and an NIHSS ≥ 5 will be evaluated as a disabling stroke. Listing 6.9 entitled *NIH Stroke Scales (NIHSS)* supports Table 6.9.

10. REFERENCES

1. Mokin, Maxim, et al. "Indications for Thrombectomy in Acute Ischemic Stroke from Emergent Large Vessel Occlusion (Elvo): Report of the SNIS Standards and Guidelines Committee." *Journal of NeuroInterventional Surgery* 11.3 (2019): 215-20.

2. San Román, L., et al. "Imaging Features and Safety and Efficacy of Endovascular Stroke Treatment: A Meta-Analysis of Individual Patient-Level Data." *The Lancet* 17.10 (2018): 895-904.