POST-APPROVAL STUDY of TRANSCAROTID ARTERY REVASCULARIZATION in PATIENTS with SIGNIFICANT CAROTID ARTERY DISEASE.

The ROADSTER 2 Study

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1 Protocol Summary

Title	POST-APPROVAL STUDY of TRANSCAROTID ARTERY REVASCULARIZATION in PATIENTS with SIGNIFICANT CAROTID ARTERY DISEASE. (The ROADSTER 2 Study)
Objective	The ROADSTER 2 Study is intended to evaluate real world usage of the ENROUTE Transcarotid Stent when used with the ENROUTE Transcarotid Neuroprotection System by physicians of varying levels of training and previous experience with the transcarotid technique.
Study Design	The ROADSTER 2 Study is an open label, single arm, multi-center post-approval Study for the treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and who are eligible for treatment with a combination of the ENROUTE Transcarotid Stent System and the ENROUTE Transcarotid NPS.
Enrollment	A minimum of 600 patients treated per protocol. Enrollment will be an entirely new cohort of patients. Additional follow-up on subjects from the ROADSTER IDE will not be included. A maximum of 30 patients per physician will be included in the first 600 patients. A physician may enroll more than 30 patients.
Investigation Site Locations	A minimum of 30 and up to a maximum of 100 sites in the United States. A maximum of 5 sites in the European Union. No more than 30% of the sites will be sites that previously enrolled in the ROADSTER study.
Primary Endpoint	The rate of procedural success through 30 days following stent implant.
Secondary Endpoints	The following secondary endpoints will be assessed 0 to 30 days: ▪ Acute device success ▪ Technical success ▪ Rate of cranial nerve injury ▪ Rate of cardiac death ▪ Rate of neurological death ▪ Rate of hierarchical ipsilateral stroke, death and MI ▪ Rate of hierarchical ipsilateral stroke, death and MI by symptom status ▪ Acute device, technical and procedural success by physician experience ▪ Acute device, technical and procedural success by physician training level ▪ Acute device, technical and procedural success by enrollment quartile
Patient Population	Patients with atherosclerotic extracranial internal carotid stenosis (ICA) with or without involvement of the contiguous common artery (CCA) determined by duplex ultrasound, CT/CTA, MR/MRA or angiography to be: Symptomatic (≥ 50% stenosis) or Asymptomatic (≥ 80% stenosis)
Planned Schedule	Commence Enrollment: Q3 2015 Complete Enrollment: End of Q1 2018 Complete 30-day Follow-Up: 30 days following last enrollment Issue FDA Final Report: Beginning of Q3 2018

15 Adjudication of Events

15.1 Clinical Events Committee (CEC)

An independent Clinical Events Committee will be assembled to review and adjudicate strokes, cranial nerve injuries, and UADEs (and their relationship to the device or procedure) events, as well as major protocol deviations affecting patient safety, that occur while a patient is enrolled in the study. The committee will be comprised of a multidisciplinary group of physicians including at least one neurologist, at least one vascular surgeon and at least one cardiologist. The committee members will not be participating in the trial and will not have an affiliation with the Sponsor, Investigators, or Study sites.

15.2 Strokes

The CEC will adjudicate all suspected strokes.

15.2.1 Major Stroke

A Major Stroke is to be defined as an increase of 5 or more in NIH Stroke Scale from baseline score and a Modified Rankin Score of ≥3.

Note: If NIH ≥4 at enrollment, any change ≥5 is considered a major stroke. If Rankin ≥3 at enrollment, and change ≥1 is considered a major stroke .

15.2.2 Minor Stroke

A Minor Stroke is defined as an increase in NIH Stroke Scale score of at most 4 points from baseline and a Modified Rankin score of at least 2.

Note: If NIH ≥4 at enrollment, any change ≤4 is considered a minor stroke

15.3 Cranial Nerve Injuries

The CEC will adjudicate all suspected cranial nerve injuries that occur within 30 days (+7 days) of the procedure.

16 Statistical Methods and Determination of Sample Size

16.1 Overview

The following section provides an outline of the statistical methods to be applied to the clinical data from this study. A Statistical Analysis Plan, containing the details for generating the analyses, will be finalized prior to any analyses being conducted.

16.1.1 Sample Size Calculation

The sample size for this clinical investigation is based on the rate of procedural success within 30 days of the stent implant. The observed rate of procedural success in the ROADSTER 2 Study will be compared to an *a priori* threshold of 85% derived from the ROADSTER Study. The

rationale for an 85% threshold is based on the lower bound of the 2-sided 95% exact binomial confidence intervals of the procedural success rates from the ROADSTER Lead-In Phase (91.0%, 95% CI 81.52%, 96.64%) and the ROADSTER Pivotal Phase (95.7%, 95% CI 90.97%, 98.42%). Given that the majority of sites that will participate in the ROADSTER 2 Study will not have participated in the ROADSTER IDE, the procedural success rate must consider outcomes from early enrollment. With an observed rate of procedural success >89% in the ROADSTER 2 Study, the results will be significant with a minimum of 600 patients, meaning the lower bound of the 2-sided 95% exact binomial confidence interval will exceed 85%. Deterministically, if 534 patients of the 600 total cases (89%) were classified as a procedural success within 30 days of the stent implant, the exact 95% lower binomial confidence limit would be 86.22%.

Estimates for the 3 categories of physicianlevel of training and experience (yes/no) will be summarized. However, given the distribution of physicians by level of training and experience will not be controlled for in this clinical investigation, it is indeterminate how informative the estimates will be.

16.2 Endpoint Analyses and Hypothesis Testing

The hypothesis testing will be focused on the proportion of patients classified as a procedural success, and to examine differences among the levels of physician training and the experience of physicians.

16.2.1 Primary Endpoint

The primary endpoint for the study is the rate of procedural success through 30 days following stent implant. The derivation of the endpoint for the primary analysis of the primary endpoint will consider all patients who undergo the procedure and in the absence of a major protocol deviation, i.e., the Per Protocol population. Patients who exit the study prior to the 30 day post-procedure evaluation who meet the definition of a procedural success based on their last observation will be counted in the analysis as a procedural success. Secondary analyses of the primary endpoint will consider alternative methods of imputation; the details of these supplemental analyses will be described in the Statistical Analysis Plan.

16.2.2 Primary Analysis of the Primary Endpoint

The dependent variable used in the primary analysis will be dichotomous and set to *Yes* if the patient is a procedural success through 30 days following stent implant and *No* if they are not a procedural success through 30 days following stent implant. Results from the analysis of the primary endpoint will be based on a 2-sided binomial test, compared to an *a priori* threshold of 85.0%. The 2-sided 95% exact binomial confidence intervals will also be presented. Patients who withdraw prior to 30 days, but at the time of withdraw were tracking to meet the definition of a procedural success, will be counted in the analysis as a procedural success.

16.2.3 Secondary Endpoint

The analyses to be conducted on the secondary endpoints are intended to provide additional supportive evidence of the efficacy and safety of the device. There are 10 secondary endpoints that will be assessed at 30 days post-procedure; each of the secondary endpoints is a dichotomous variable:

- Acute device success
- Technical success
- Rate of cranial nerve injury

- Rate of cardiac death
- Rate of neurological death
- Rate of hierarchical ipsilateral stroke, death and MI
- Rate of hierarchical ipsilateral stroke, death and MI by symptom status
- Acute device, technical and procedural success by physician experience
- Acute device, technical and procedural success by physician training level
- Acute device, technical and procedural success by enrollment quartile

16.3 Statistical Methods

The pre-procedure observations will serve as the *baseline* values for calculating post procedure changes from baseline. Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS software version 9.2 or higher. The statistical analyses will be based on data pooled across *Sites* in aggregate; a secondary tabulation will be prepared separately for the US and Non-US sites. Continuous demographic parameters, such as the age of the patient at the time of enrollment, will be summarized for the Per-Protocol population using descriptive statistics (N, mean, median, standard deviation, minimum and maximum value, and 95% 2-sided confidence limits). Continuous demographic parameters will be compared among the 3 levels of physician training and experience using a 1-factor (physician training [1, 2 or 3]; physician experience [participation in ROADSTER 1 or no participation in ROADSTER 1) analysis of variance model. Contrast statements will be used to evaluate the individual pair wise comparisons (Level 1 vs. Level 2, Level 1 vs. Level 3, and Level 2 vs. Level 3; participation in ROADSTER 1 vs no participation in ROADSTER 1). Categorical demographic parameters, such as gender, will be summarized as a proportion of the Per-Protocol population using Clopper-Pearson 95% 2-sided confidence limits. The categorical demographic parameters will be compared using a Mantel-Haenszel test stratified on physician level of training (1, 2, or 3) and separately by physician experience (participation in ROADSTER 1 vs no participation in ROADSTER 1). Additionally, a generalized linear model (PROC GENMOD) will be used to evaluate the main effect of physician level of experience, specifying the distribution as either binomial or multinomial. Clinical and high risk factors will also be summarized as a proportion of the Per-Protocol population with Clopper-Pearson 95% 2-sided confidence limits. In addition to the overall summary of the individual factors, separate summaries will be generated by physician experience and level of training. Comparisons will be made among the 3 levels of physician training and physician experience (participation in ROADSTER 1 vs no participation in ROADSTER 1), depending on the type and distribution of the parameter.

Data obtained during the neurological examination, including data from the NIH Stroke Scale, Modified Rankin Scale and Cranial Nerve Palsy Assessment will be summarized at each time point using descriptive statistics. Separate summaries will be generated by level of physician training and experience and compared using a 1-factor (physician level of training [1, 2 or 3]) and a 1-factor (experience: participation in ROADSTER 1 vs. no participation in ROADSTER 1) analysis of variance model. Contrast statements will be used to evaluate the individual pair wise comparisons (Level 1 vs. Level 2, Level 1 vs. Level 3, and Level 2 vs. Level 3).

Specific algorithms for imputing missing or partially missing dates will be discussed in the SAP. Derived data will be identified in the individual patient data listings. Imputed data for dates will not

be incorporated into the case report form datasets. Imputed data for dates will be used in the preparation of the derived datasets.

16.4 Populations for Analysis

The Per-Protocol population is defined as patients who sign an informed consent, undergo the study procedure, independent of the success of the procedure, and with the absence of major protocol deviations. Patients who sign an informed consent, however fail to undergo the study procedure, will not be included in the Per-Protocol population. A maximum of 30 patients treated per protocol per physician can contribute to the 600 patient minimum. A physician may enroll more than 30 patients.

The primary endpoint and all secondary endpoints will be analyzed based on the Per-protocol population. All available data on the Per-Protocol patients who enrolled in the study will be included. Any subject not meeting the Inclusion/Exclusion criteria will be tabulated but not included in the primary endpoint analysis.

17 Data Collection

Data will be entered into a validated electronic data management system. Data fields in the selected electronic data management system used will be aligned such that it overlaps with the appropriate data fields for the post-approval study as derived from the ROADSTER IDE.

18 Sponsor Responsibilities

18.1 Selection of Clinical Investigators and Sites

All US sites participating in the ROADSTER 2 Study will be limited to institutions with current CMS carotid stent certification. Institutions will be compensated for complete and accurate data collection.

18.2 Training of Investigators and Site Personnel

Investigators and site personnel will be trained on the following aspects of the clinical study:

- Protocol
- Case Report Forms
- Risks and Benefits
- Reporting Responsibilities
- Informed Consent
- Device Usage
- Device Instructions for Use
- Confidentiality

Investigator responsibilities are further detailed below.