PROST: pRESET for Occlusive Stroke Treatment

PRODUCT UNDER INVESTIGATION:

pRESET Thrombectomy Device

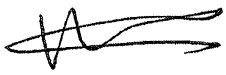
PROTOCOL NUMBER
pCT-001-19

STUDY SPONSOR
phenox Inc.
9842 Research Drive
Irvine CA, 92613

PREPARED BY
Bruce C. Stouch, Ph.D.
BCS Statistical Solutions LLC

DATE AND VERSION
July 13, 2022 (Version 6.0)

APPROVALS

Name and Title	Signature	Date
Gary Brogan Director of Regulatory Affairs Phenox Inc.		July-27-2022
Richard P. Chiacchierini, Ph. D. DSMB Biostatistician		
Bruce C. Stouch, Ph.D. Biostatistician		27 Jul 2022
Tine Willems, Ph.D. Biostatistician		

STATISTICAL ANALYSIS PLAN

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SUMMARY OF CHANGES

Version 3.0 was the first version of the plan that was put into production. Versions 1 and 2 of the Statistical Analysis Plan were internal versions that evolved during the finalization of the study protocol.

STATISTICAL ANALYSIS PLAN REVISION HISTORY		
Document Version	**Document Date**	**Reason for Revision**
4.0	February, 2020	Modification to the interim assessment plan. Modification to the testing strategy for the primary and secondary endpoints. Addition of the tables, figures, and listings to be generated.
5.0	April 30, 2020	The follow-up assessment for NIH Stroke Scale at the 30 day and 90 day timeframe is being moved to optional
6.0	June 30, 2022	1. Clarification that the covariates to be used for the imputation will come from the randomization system that has all of the strata. This is necessary because of patients who were randomized but did not undergo the study procedure. 2. Section 3.2.2: Clarify that the analysis will be conducted using a proportional odds model (ordinal logistic regression) with an assumed common odds ratio of improvement on the mRS, is the confidence interval of the upper bound of the odds ratio less than 0.875 and not using a with chi-square test of the difference in linear trends 3. Section 8.1: Screen failures will not be reported in Table 14.1.1 and Table 14.1.1.1. Table 14.1.1.2 will be changed from Reasons for Screen Failures to Reasons Patients Did Not Undergo the Study Procedure. 4. Section 8.1: Listing 16.3.1 entitled Protocol Violations has been removed. Protocol violations are not assessed; protocol deviations are assessed. 5. Addition of Table 14.1.6.1 entitled Comparison of the mRS Scores at the Time of Admission with the Randomization Stratification Factors Introduced into the Model as Covariates by Randomized Treatment Assignment (observed data). Results will be presented using the ITT population. 6. The endpoint analysis tables will be generated for all three populations: ITT, PP, and AT. 7. The derivation for each endpoint, the source dataset, and the variable has been added for each endpoint. 8. The order for analysis of the 4 secondary endpoints using the step down approach to control for inflation of the type 1 error rate will be as follows: Secondary endpoint 2, 1, 3 and 4.

1. LIST OF ABBREVIATIONS

Abbreviations		
Abbreviation	Abbreviated Term	Definition
AAE	Anticipated Adverse Event	Any decline away from the patient's baseline health, whether related to the investigational device, the procedure or the disease that is predefined in the Investigational Plan, CRFs, and Instructions For Use.
ADE	Adverse Device Effect	Any untoward and unintended response to a medical device including insufficiencies or inadequacies in instructions for use or deployment of the device.
AE	Adverse Event	Any decline away from the patient's baseline health. Any decline from the patient's pre-treatment condition that occurs during the course of the clinical Study, after study enrollment, whether related to the investigational device, the procedure or the disease. Treatment includes all investigative or commercially approved products administered according to the Investigational Plan.
AICH	Asymptomatic Intracranial Hemorrhage	Any intracranial hemorrhage within 24 hours not meeting the criteria for symptomatic intracranial hemorrhage.
AIS	Acute Ischemic Stroke	Focal symptoms due to cerebral infarction from an arterial occlusion.
CEC	Clinical Events Committee	Independent committee responsible for the review and validation of all complications that occur over the course of the Study.
DICOM	Digital Imaging and Communications in Medicine	The standard foundation for imaging and image management; A global information-technology standard designed to ensure the interoperability of systems used to produce, store, display, process, send, retrieve, query, or print medical images and derived structured documents.
DSMB	Data Safety and Monitoring Board	An independent data monitoring committee, established by the sponsor, to assess at intervals, the progress of a clinical trial, the safety data and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify or stop a trial.
DWI	Diffusion Weighted Imaging	Imaging obtained using magnetic resonance sequences that measure diffusion properties of water within tissue.
eCRF	Electronic Case Report Form	An electronic document designed to record all of the protocol requested information to be reported to the sponsor on each study patient. eCRFs are "living documents" in the respect that new information on the patient is continually gathered throughout the study.
FR	Flow Restoration	Restore flow through a vessel that is occluded by blood clot.

Abbreviations

Abbreviation	Abbreviated Term	Definition
GCP	Good Clinical Practice	The regulations enforced in the US by the FDA's bioresearch monitoring program for medical devices, consisting of 21 CFR 812, -50 and -56. The GCP requirements are also stated in "Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, ICH, April 1996: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported are credible and accurate, and that the rights, integrity and confidentiality of trial patients are protected.
HIPAA	Health Insurance Portability and Accountability Act	Health Insurance Portability and Accountability Act of 1996. Title II of the Act, "Administrative Simplification" refers in large part to federal privacy rules that require health care providers and others to obtain written authorization from patients or their legally authorized representatives before using or disclosing their "Protected Health Information" (PHI) for any purposes other than treatment, billing, quality assurance and education.
ICF	Informed Consent Form	The written, signed and dated document that provides objective evidence of the process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate (21 CFR 50).
ICH	International Conference for Harmonization	An Organization whose main purpose is to achieve greater harmonization to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.
IDE	Investigational Device Exemption	An approved IDE permits a device that would otherwise be required to comply with a performance standard or would require a premarket approval to be shipped lawfully for the purpose of conducting investigations of that device (21 CFR 812).
I/E	Inclusion/Exclusion Criteria	A list of conditions that would include or exclude a patient from enrolling/participating in a clinical study as outlined in the study protocol.
IEC	Independent Ethics Committee	An independent body, constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human patients involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities and the methods and material to be used in obtaining and documenting informed consent of the trial patients.
INR	International Normalized Ratio	Ratio that measures the time it takes for blood to clot and compares it to a reference normal value.
IP	Investigational Plan	The clinical protocol and associated documents whose required composition is described in 21 CFR 812.25.
IRB	Institutional Review Board	Any board, committee, or other group formally designated by an institution to review biomedical research involving patients and established, operated and functioning in conformance with 21 CFR 56.

Abbreviations

Abbreviation	Abbreviated Term	Definition
ISO	International Organization for Standardization	International standard-setting body composed of representatives from various national standards organizations.
ITT	Intent-to-Treat	The ITT population includes all patients with data for a given endpoint and are assessed according to randomized assignment regardless of the treatment actually received
IV t-PA	Intravenous Tissue Plasminogen Activator	Medical treatment of myocardial infarction with ST-elevation (STEMI), acute ischemic stroke (AIS), acute massive pulmonary embolism, and central venous access devices (CVAD) administered intravenously. t-PA is an enzyme (serine protease) found in endothelial cells that line the blood vessels that converts plasminogen into plasmin, an enzyme responsible for blood clot breakdown.
IVRS	Interactive Voice Response System	Accessed by telephone, it is a system that randomly assigns the patient to a treatment arm based on the pre-determined randomization algorithm.
IWRS	Interactive Web Response System	Accessed by internet, it is a system that randomly assigns the patient to a treatment arm based on the pre-determined randomization algorithm.
MedDRA	Medical Dictionary for Regulatory Activities	Standardized medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorized for sale. Products covered by the scope of MedDRA include pharmaceuticals, vaccines and drug-device combination products.
mRS	Modified Rankin Score	Scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke. 0 No symptoms at all 1 No significant disability despite symptoms; able to carry out all usual duties and activities 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 Moderate disability; requiring some help, but able to walk without assistance 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 Dead
NIHSS	National Institute of Health Stroke Scale	Method for quantifying neurologic deficits developed by the National Institutes of Health. It is used to assess the severity of a stroke.
OC/RDC	ORACLE Clinical/ Remote Data Capture	EDC system that will be deployed to support data collection for this study.

Abbreviations

Abbreviation	Abbreviated Term	Definition
PTT	Partial Thromboplastin Time	Measure of how long it takes for blood to clot. This test is used to determine if a patient has bleeding or clotting problems.
PWI	Perfusion weighted imaging	Imaging obtained using contrast that measures the brain perfusion including vascular transit time, cerebral blood volume, and cerebral blood flow.
QALY	Quality-adjusted life year	A measure that takes into account both the quantity and quality of life generated by healthcare interventions. It is the arithmetic product of life expectancy and a measure of the quality of the remaining life-years
RAPID	RApid processing of PerfusIon and Diffusion	A system that computes quantitative perfusion maps (cerebral blood volume, CBV; cerebral blood flow, CBF; mean transit time, MTT; and the time until the residue function reaches its peak, T(max)) using deconvolution of tissue and arterial signals.
SAE	Serious Adverse Event	Adverse Event that led to death or serious deterioration in the health of a patient that resulted in a life threatening illness or injury, permanent impairment of a body structure or a body function, hospitalisation or prolongation of existing hospitalisation, medical or surgical intervention to prevent permanent impairment to a body structure or a body function or is a congenital anomaly/birth defect.
SICH	Symptomatic Intracranial Hemorrhage	Any PH1, PH2, RIH, SAH, or IVH associated with a 4 points or more worsening on the NIHSS within 24 hrs. PH1: Hematoma within ischemic field with some mild space-occupying effect but involving ≤ 30% of the infarcted area. PH2: Hematoma within ischemic field with space-occupying effect involving >30% of the infarcted area RIH: Any intraparenchymal hemorrhage remote from the ischemic field IVH: Intraventricular hemorrhage SAH: Subarachnoid hemorrhage
SOP	Standard Operating Procedure	A document that defines a process that needs to be followed during the course of the study.
TICI	Thrombolysis in Cerebral Infarction Perfusion Categories	0 = No perfusion. No antegrade flow beyond the point of occlusion. 1 = Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion 2A = Perfusion of less than half of the vascular distribution of the occluded artery (e.g., filling and perfusion through 1 M2 division) 2B = Perfusion of half or greater of the vascular distribution of the occluded artery (e.g., filling and perfusion through 2 or more M2 divisions) 3 = Full perfusion with filling of all distal branches

Abbreviations		
Abbreviation	Abbreviated Term	Definition
UADE	Unanticipated Adverse Device Effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the Investigational Plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.
ULN	Upper Limit of Normal	Upper limit within a particular range.

2. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to prospectively outline the types of analyses and presentations of the data that will form the basis for conclusions regarding this clinical investigation. The analyses defined in this plan should answer the safety and effectiveness objectives outlined in the protocol, and explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices for biostatistical analysis in the medical device industry.

This document contains information to support the generation of a Clinical Study Report (CSR) for Clinical Protocol pCT-001-19, including detailed descriptions of the statistical methods to be applied, as well as the analysis summary tables and figures and patient data listings intended to present the analysis results.

The SAP is a forward-thinking document. The derivation of the endpoints that require data to be pulled from multiple locations involving several steps may be revised, depending on the external adjudication and image files; any such deviations will be clearly defined in the CSR and the Reviewer's Guide. After the patient was consented, the clot may have resolved and proceeding with the study procedure was no longer medically indicated. Therefore, a procedure date is not available for all of the enrolled patients. The SAP is specific to the anchoring date used for the individual calculations.

Throughout the SAP, reference will be made to the following 3 sources:

Electronic Data Capture (EDC) files containing the case report form data entered at the investigational site
Clinical Event Committee (CEC) files containing the adjudicated safety events; these files will be integrated into the EDC system
Stroke Drop / Core Laboratory file: External blinded image analysis file containing the independent radiographic determination for target vessel revascularization (eTICI).

The planned analyses identified in this SAP may be included in regulatory submissions, medical presentations and manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc or unplanned analyses that are performed but not identified in this SAP will be clearly identified in the CSR. The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and the International Conference on Harmonization Guidance on Statistical Principles for Clinical Trials.

3. STUDY OBJECTIVES AND ENDPOINTS

This prospective, multi-center randomized adaptive clinical trial is composed of 3 phases: screening, treatment, and follow-up. The objectives and endpoints will be based on the data collected during the treatment and follow-up period. There is a single primary effectiveness endpoint and a primary safety endpoint. There are 4 secondary endpoints that will be evaluated statistically in hierarchical order.

3.1. Study Objectives

The study objective is to quantify the safety and effectiveness of pRESET for the treatment of acute ischemic stroke within 8 hours of symptom onset (defined as the time patient was last seen "well" and without stroke symptoms) due to large vessel occlusion (LVO). The safety and effectiveness results from the pRESET treatment group will be compared to the predicate device: Solitaire™ revascularization device (Medtronic).

The primary effectiveness objective will be based on the global disability index assessed via a blinded evaluation using the Modified Rankin Scale (mRS) ≤ 2 at 90 days after the index procedure. The primary safety objective will be based on device-related or procedure-related symptomatic intracerebral hemorrhage (sICH) within 24 hours (-8/+12 hours) of the study index procedure.

The following section defines the specific endpoints and research questions that will be addressed through the course of this clinical investigation, mapped to the individual variables.

3.2. Study Endpoints

The individual endpoints and variables are listed below. Reference is made to 2 nominal time points: *baseline* and *Day 7 / hospital discharge* following the index procedure. *Baseline* is defined as a measurement or observation recorded prior to the index procedure following the index stroke. *Day 7 / hospital discharge* is defined as the 7th day post procedure with the day of the procedure counted as Day 1. If discharge is prior to Day 7 post-treatment, the measurement or observation recorded on the day of discharge will be the value used in the analysis. If discharge is after Day 7 post-treatment, the measurement or observation recorded on Day 7 will be the value used in the analysis.

3.2.1. Primary Study Endpoints

The primary effectiveness and safety endpoints will be evaluated simultaneously. If the primary effectiveness endpoint is met (pRESET non-inferior to Solitaire), the secondary endpoints will be examined in rank order. The testing strategy is defined in Section 7 of this Statistical Analysis Plan. The results will be presented for all 3 analysis populations: the intention-to-treat (ITT) population is the primary population for determining the results from this study. The per-protocol population and the as-treated populations will be used to frame the sensitivity analyses.

The **primary effectiveness endpoint** is an assessment of global disability assessed via the blinded evaluation of the proportion of patients with a Modified Rankin Scale (mRS) ≤ 2 recorded 90 days after the index procedure. The proportions will be compared between the pRESET and Solitaire treatment arms.

- The raw source dataset for this endpoint will be the SPSS_CLINEVAL4 dataset from the EDC system. The variable within the dataset is named CLINEVAL4: mRS at 90 days.

The **primary safety endpoint** is an assessment of device-related or procedure-related symptomatic intracerebral hemorrhage (sICH) within 24 hours (-8/+12 hours) of the index procedure.

sICH will be defined as based on the SITS-MOST criteria: local or remote parenchymal hemorrhage type 2 on the post-treatment imaging scan, combined with 1) a neurologic deterioration of 4 points or more compared to baseline NIHSS or the lowest NIHSS value between baseline and 24 hr. or 2) death within 24 hrs. Type 2 indicates a hematoma exceeding 30% of the infarct, with substantial space occupying effect.

Local or remote parenchymal hemorrhage type 2 will come from the external Stroke Drop file. The variable within the dataset is named 24 Hemorrhage Type PH-2.

The raw source dataset for the NIHSS baseline score will come from the SPSS_MH dataset from the EDC system. The variable within the dataset is named NIHSS at Admission in Site.

The raw source dataset for the NIHSS score at 24 hrs. will be the SPSS_CLINEVAL1 dataset from the EDC system. The variable within the dataset is named NIHSCALE] NIH Stroke Scale.

- The raw source dataset for mortality will be the SPSS_DS dataset from the EDC system. The reason the *Patient Exited the Study* will be *Subject Death* and the *Date of Death* will be used to determine if it occurred within 24 hrs. of the date informed consent was obtained.

The raw source dataset for the determination of the sICH event as being either device-related or procedure-related will be the AECECCON dataset from the EDC system. The variable within the dataset is named CECCON [Relationship to Study Procedure (Consensus) Display = YES or Relationship to Study Device (Consensus) Display = YES].

The proportions will be compared between the pRESET and Solitaire treatment arms.

3.2.2. Secondary Effectiveness Study Endpoints

There are 4 secondary endpoints defined below in rank order. The results will be presented for all 3 analysis populations (Section 6): the ITT population is the primary population for determining the results from this study. The per-protocol population and the as-treated populations will be used to frame the sensitivity analyses.

The **first** secondary effectiveness endpoint will be based on the proportion of patients with eTICI 2b50 or greater flow in the target vessel post-procedure with ≤3 passes of the assigned study device. The maximum number of allowed passes under protocol is 3. The proportions will be compared between the pRESET and Solitaire treatment arms.

- The source for this endpoint will come from the external Stroke Drop file. The variables within the dataset are named Pass 1 eTICI, Pass 2 eTICI, and Pass 3 eTICI. The best eTICI score, up to a maximum of 3 passes, will be used for the analysis of eTICI.

The **second** secondary effectiveness endpoint will be based on the proportion of patients with eTICI 2c or greater following the first pass of the assigned study device. The proportions will be compared between the pRESET and Solitaire treatment arms.

- The source for this endpoint will come from the external Stroke Drop file. The variables within the dataset is named Pass 1 eTICI.

The **third** secondary effectiveness endpoint will be based on overall mortality at 90 days following the index stroke. The proportion of patients who die on or before day 90 will be compared between the pRESET and Solitaire treatment arms.

- The raw source dataset for mortality will be the SPSS_DS dataset from the EDC system. The reason the *Patient Exited the Study* will be *Subject Death* and the *Date of Death* will be used to determine if it occurred within 90 days following the index stroke.

The **fourth** effectiveness secondary endpoint is the modified Rankin Scale (mRS) shift at 90 days following the index stroke. The analysis is a chi-square test of the difference in linear trends in ordinal mRS outcomes at 90 days post procedure between treatment groups using a proportional odds model (ordinal logistic regression).

- The raw data source will be the SPSS_MH dataset from the EDC system. The name of the variable within the dataset is Baseline mRS Score. The raw data source for the 90 Day mRS Score will be the SPSS_CLINEVAL4 dataset from the EDC system. The name of the variable within the dataset is CLINEVAL4: mRS at 90 days.

3.2.3. Pre-specified Exploratory Endpoints

There are 9 tertiary exploratory endpoints that will be evaluated. The results will be presented for all 3 analysis populations (Section 6): the ITT population is the primary population for determining the results from this study. The per-protocol population and the as-treated populations will be used to frame the sensitivity analyses.

The **first** exploratory endpoint is an assessment of global disability assessed via the blinded evaluation of the proportion of patients with a Modified Rankin Scale (mRS) ≤ 1 recorded 90 days after the index stroke. The raw data source for the 90 Day mRS Score will be the SPSS_CLINEVAL4 dataset from the EDC system. The name of the variable within the dataset is CLINEVAL4: mRS at 90 days. The proportions will be compared between the pRESET and Solitaire treatment arms.

The **second** exploratory endpoint will be based on the proportion of patients with eTICI 2c or greater within ≤3 passes (last pass) of the assigned study device based on the best eTICI score. The proportions will be compared between the Preset and Solitaire treatment arms.

- The source for this endpoint will come from the external Stroke Drop file. The variables within the dataset are named Pass 1 eTICI, Pass 2 eTICI, and Pass 3 eTICI. The value of the best eTICI score, up to a maximum of 3 passes, will be used for the analysis of eTICI. The proportions will be compared between the pRESET and Solitaire treatment arms.

The **third** exploratory endpoint will be based on the best eTICI score within ≤3 passes eTICI 2b50 or greater or greater proportions by randomized study device. The proportions will be compared between the pRESET and Solitaire treatment arms.

- The source for this endpoint will come from the external Stroke Drop file. The variables within the dataset are named Pass 1 eTICI, Pass 2 eTICI, and Pass 3 eTICI.

The **fourth** exploratory endpoint will be based on the proportion of target vessels with first-pass eTICI 2b50, 2b67, 2c or 3 by randomized study device. The proportions will be compared between the pRESET and Solitaire treatment arms.

- The source for this endpoint will come from the external Stroke Drop file. The variables within the dataset are named Pass 1 eTICI. The raw data source for the target vessels will also be the Stroke Drop file; the locations are specified below:

  Distal Bas
  Distal ICA
  Distal M1
  Distal M2
  Proximal M1
  Proximal M2

The **fifth** exploratory endpoint will be based on the proportion of patients with "early response" at Day 7/Discharge (whichever is earlier), defined as a NIHSS reduction of ≥10 points from baseline or an NIHSS score 0 or 1. The proportions will be compared between the pRESET and Solitaire treatment arms.

- The raw data source for the baseline NIHSS will be the SPSS_MH dataset from the EDC. The variable name is NIHSS at Admission in Site.
- The raw data source for the 7 Day/Discharge NIHSS will be the SPSS_CLINEVAL2 dataset from the EDC. The variable name is NIH Stroke Scale.

The **sixth** exploratory endpoint will be based on the proportion of patients with all intracranial hemorrhages using the Heidelberg Bleeding classification by randomized study device. The proportions will be compared between the pRESET and Solitaire treatment arms.

- The source for this endpoint will come from the external Stroke Drop file. The variables within the dataset are named 24h Hemorrhage and Other1 Hemorrhage through Other9 Hemorrhage.

The **seventh** exploratory endpoint will be based on stroke-related mortality 90 days after the index stroke by randomized study device.

The raw source dataset for the date of the index stroke will be the SPSS_MH dataset from the EDC system. The variable name in the dataset is Date of stroke onset.

The raw source dataset for mortality will be the SPSS_DS dataset from the EDC system. The reason the *Patient Exited the Study* will be *Subject Death* and the *Date of Death* will be used to determine if it occurred within 90 days of the index stroke.

The **eighth** exploratory endpoint will be based on the incidence of *neurological deterioration* from the baseline NIHSS score through Day 7, or at the time of discharge if discharge is prior to Day 7 post-treatment. *Neurological deterioration* is defined as ≥ 4-point increase in the NIHSS score from the baseline score. The proportions will be compared between the pRESET and Solitaire treatment arms.

The raw source dataset for the NIHSS baseline score will come from the SPSS_MH dataset from the EDC system. The variable within the dataset is named NIHSS at Admission in Site.
The raw source dataset for the NIHSS score at through Day 7 / Discharge will be the SPSS_CLINEVAL2 dataset from the EDC system. The variable within the dataset is named NIHSCALE: NIH Stroke Scale.

The **ninth** exploratory endpoint will be based on a comparison of the incidence of procedure-related and device-related serious adverse events (PRSAEs and DRSAEs) through 24 (-6/+24) hours post-procedure.

The following logic will be followed to derive the variable for analysis from the AECECCON file in the EDC: [CECCON] Was it Serious (Consensus) and either device or procedure related.

Each event will be adjudicated by the clinical events committee, and defined as:

a. Vascular perforation (procedure and/or device related)
   – Source is the Stroke Drop File and the EDC system. If there is a record of a perforation in either file, the event will be counted.

b. Intramural arterial dissection (procedure and/or device related)
   – Source is the Stroke Drop File and the EDC system. If there is a record of a dissection in either file, the event will be counted.

c. Embolization to a new territory (procedure and/or device related)
   – Source is the Stroke Drop File

d. Access site complication requiring surgical repair or blood transfusion (procedure related)
   -Source is the EDC dataset SPSS_AE [(S)AE] Onset Interval Display filtered to "Procedure". All procedure onset events will be manually reviewed for access site complications requiring surgical repair or blood transfusion

e. Intra-procedural mortality (procedure and/or device related)

   - Source is the EDC dataset SPSS_AE [(S)AE] Onset Interval Display filtered to "Procedure" and [S)AE] Final Outcome Display filtered to "Death"

   - The Date of Death, sourced from the EDC dataset SPSS_DS, will be checked against all procedure onset events ending in death to determine if it occurred through 24 (-6/+24) hours post-procedure.

f. Device failure (in vivo breakage) (device related)

   - Source is the EDC dataset SPSS_PRODEVOF with manual review of the Narrative to Describe Issue, Observation or Malfunction to identify in vivo breakage

g. Any other complications adjudicated by the CEC to be related to the procedure (procedure related)

3.2.4. Research Questions

The primary and secondary endpoints will be evaluated for substantiation of potential label claims. The individual research questions that map to these endpoints, and how the results will be interpreted, is presented below.

Primary Effectiveness Research Question 1 (PERQ1)

The primary effectiveness endpoint of this study maps to the primary effectiveness objective and addresses the following research question:

After 90 days following the procedure, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in global disability (mRS ≤ 2) above the a priori threshold of -12.5%?

● Interpretation: If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in global disability is numerically greater than -12.5%, pRESET will be considered non-inferior to Solitaire.

Primary Safety Research Question 1 (PSRQ1)

The primary safety endpoint of this study maps to the primary safety objective and addresses the following research question:

Within 24 hours (-8/+12 hours) after the study procedure, is the upper bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) with device-delated or procedure-related SICH below the a priori threshold of 5%?

● Interpretation: If the upper bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in global disability is numerically less than 5%, pRESET will be considered non-inferior to Solitaire.

Secondary Research Question 1 (SRQ1)

The non-inferiority margin has been pre-specified to be -12.1% based on the peer-reviewed literature (ref. Section 4.3). The research question for the first secondary endpoint is presented below:

*Following a **maximum of 3 passes** (last pass) of the assigned study device, and based on the best eTICI result within ≤3 passes, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50 or greater flow in the target vessel post-procedure above the a priori threshold of -12.1%?* The best eTICI result within ≤3 passes will be used in the analysis.

● Interpretation: If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50 or greater flow in the target vessel post-procedure is numerically greater than -12.1%, pRESET will be considered non-inferior to Solitaire.

Secondary Research Question 2 (SRQ2)

The non-inferiority margin has been pre-specified to be -12.1% based on the peer-reviewed literature (ref. Section 4.3). The research question for the second secondary endpoint is presented below:

*Following the **first pass** of the assigned study device, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2c or greater flow in the target vessel post-procedure above the a priori threshold of -12.1%?*

● Interpretation: If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2c or greater flow in the target vessel post-procedure is numerically greater than -12.1%, pRESET will be considered non-inferior to Solitaire.

Secondary Research Question 3 (SRQ3)

The non-inferiority margin has been pre-specified to be 10%; the rationale is presented in Section 4.3. The research question for the third secondary endpoint is presented below:

Ninety days following the index stroke, is the upper bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in mortality below the a priori threshold of 10%?

● Interpretation: If the upper bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in mortality is numerically less than 10%, pRESET will be considered non-inferior to Solitaire.

Secondary Research Question 4 (SRQ4)

The research question for the fourth secondary endpoint is presented below:

After 90 days following the stroke, using a proportional odds model (ordinal logistic regression) with an assumed common odds ratio of improvement on the mRS, is the confidence interval of the upper bound of the odds ratio less than 0.875, suggesting the shift towards better outcomes across the entire spectrum of disability is more than 12.5% better with Solitaire compared to pRESET*?*

● Interpretation:

This analysis will determine if endovascular mechanical thrombectomy performed with the 2 devices is equivalent using a proportional odds model (ordinal logistic regression) with an assumed common odds ratio of improvement on the mRS. If the confidence interval of the upper bound of the odds ratio is greater than 0.875, suggesting the shift towards better outcomes across the entire spectrum of disability is not more than 12.5% better with Solitaire compared to pRESET, non-inferiority will have been established.

Exploratory Endpoint 1 (EE1)

The research question for this endpoint is presented below:

After 90 days following the stroke, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in global disability (mRS ≤ 1) above the a priori threshold of -12.5%?

● Interpretation: If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in global disability is numerically greater than -12.5%, pRESET will be considered non-inferior to Solitaire.

Exploratory Endpoint 2 (EE2)

The research question for this endpoint is presented below:

Following the best eTICI result within ≤3 passes *of the assigned study device, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2c or greater flow in the target vessel post-procedure above the a priori threshold of -12.1%?* The best eTICI result within ≤3 passes will be used in the analysis.

● Interpretation: If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2c or greater flow in the target vessel post-procedure is numerically greater than -12.1%, pRESET will be considered non-inferior to Solitaire.

Exploratory Endpoint 3 (EE3)

The research question for this endpoint is presented below:

Following the final pass of the assigned study device, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50 or greater flow in the target vessel post-procedure above the a priori threshold of -12.1%?

● Interpretation: If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50 or greater flow or greater flow in the target vessel post-procedure is numerically greater than -12.1%, pRESET will be considered non-inferior to Solitaire.

Exploratory Endpoint 4 (EE4)

The research question for this endpoint is presented below:

Following the first pass of the assigned study device, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50, 2b67, 2c or 3 flow in the target vessel post-procedure above the a priori threshold of -12.1%?

● Interpretation: If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50 and 2c flow in the target vessel post-procedure is numerically greater than -12.1%, pRESET will be considered non-inferior to Solitaire.

Exploratory Endpoint 5 (EE5)

The research question for this endpoint is presented below:

Does the 2-sided 95% binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients classified as early responders at Day 7/Discharge (whichever is earlier), contain zero?

● Interpretation: An early responder is a patient with a NIHSS drop of ≥10 points from baseline or an NIHSS score 0 or 1 at Day 7 or Discharge from the hospital (whichever is earlier). If the 2-

sided 95% confidence interval of the difference (pRESET minus Solitaire) contains zero, pRESET will be considered not significantly different from Solitaire. If the upper bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is less than zero, the proportion of early responders pRESET will be considered significantly lower compared to Solitaire. If the lower bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is greater than zero, the proportion of early responders with pRESET will be considered significantly higher compared to Solitaire.

Exploratory Endpoint 6 (EE6)

The research question for this endpoint is presented below:

Does the 2-sided 95% binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients who experience intracranial hemorrhages contain zero?

- Interpretation: If the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) contains zero, pRESET will be considered not significantly different from Solitaire. If the upper bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is less than zero, the proportion of patients with intracranial hemorrhage with pRESET will be considered significantly lower compared to Solitaire. If the lower bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is greater than zero, the proportion of patients with intracranial hemorrhage with pRESET will be considered significantly higher compared to Solitaire.

Exploratory Endpoint 7 (EE7)

The research question for this endpoint is presented below:

Does the 2-sided 95% binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients who die within 90 days of the index stroke as a result of a stroke-related event contain zero?

- Interpretation: If the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) contains zero, pRESET will be considered not significantly different from Solitaire. If the upper bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is less than zero, the proportion of patients who die within 90 days of the index stroke with pRESET will be considered significantly lower compared to Solitaire. If the lower bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is greater than zero, the proportion of patients who die within 90 days of the index stroke with pRESET will be considered significantly higher compared to Solitaire.

Exploratory Endpoint 8 (EE8)

The research question for this endpoint is presented below:

Does the 2-sided 95% binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients classified as having neurological deterioration contain zero?

Neurological deterioration is defined as ≥ 4-point increase in the NIHSS score from the baseline score.

● Interpretation: If the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) contains zero, pRESET will be considered not significantly different from Solitaire. If the upper bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is less than zero, the proportion of patients with neurological deterioration with pRESET will be considered significantly lower compared to Solitaire. If the lower bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is greater than zero, the proportion of patients with neurological deterioration with pRESET will be considered significantly higher compared to Solitaire.

Exploratory Endpoint 9 (EE9)

The research question for this endpoint is presented below:

Does the 2-sided 95% binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients who experience a procedure-related and/or device-related serious adverse events (PRSAEs and DRSAEs) through 24 (-6/+24) hours post-procedure between the randomized treatment groups contain zero?

● Interpretation: If the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) contains zero, pRESET will be considered not significantly different from Solitaire. If the upper bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is less than zero, the proportion of patients who experience the event of interest with pRESET will be considered significantly lower compared to Solitaire. If the lower bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is greater than zero, the proportion of patients who experience the event of interest with pRESET will be considered significantly higher compared to Solitaire.

4. STUDY OVERVIEW

4.1. Study Design

The PROST study is a prospective, multi-center randomized adaptive design where the primary effectiveness endpoint will assessed via a blinded evaluation of the Modified Rankin Scale (mRS). Up to 20 study centers may participate in this study in the USA and Germany. Each participating clinical site will have 2 teams:

- an **unblinded team**, consisting of treating physicians and study coordinator who care for the patient/patient up to hospital discharge, and
- a **blinded team**, consisting of a neurologist with stroke expertise and a separate study coordinator. The blinded team performs all study assessments during and after hospital discharge (e.g., 24 hours, Day 7/Discharge (whichever is earlier), and 30 and day 90 visits). The operational details for maintaining the blinding are described in the study-specific standard operating procedure (SOP).

A pre-specified interim assessment for conditional power (CP) for potential sample size readjustment will be performed by the independent DSMB after 50% of the minimum target sample size (214/2: 107 patients) have been randomized and completed the day 90 evaluation or prematurely discontinue from the study. This DSMB assessment may lead to a recommendation to increase enrollment to the maximum target sample size of 340 patients, or discontinue enrollment for futility (CP<37%). There will be no adjustment for conducting the interim assessment for sample size adjustment.

The purpose of this trial is to provide confirmatory clinical evidence that the pRESET Thrombectomy Device provides benefits similar to those of the predicate device, Solitaire, for LVO strokes within 8 hours of symptom onset. A -12.5% non-inferiority margin (NIM) will be used to examine the lower bound of the 1-sided 95% exact binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with a 90 day mRS of 0-2 (primary endpoint).

4.2. Study Device

The pRESET Thrombectomy Device is a mechanical thrombectomy device mounted on the end of a delivery wire. The device is designed to allow the treating physician to remove blood clots from occluded cerebral arteries in the setting of acute cerebral stroke.

4.3. Justification for the Non-Inferiority Margin

A method to combine data from several studies to obtain upper and lower bounds for the rates of success is the inverse variance weighting method developed by Fleiss (1993) and later provided in Fleiss et al. (2003). This method has been recommended by the Food and Drug Administration as a means to provide boundaries that may be used as performance goals, margins of non-inferiority, or margins of equivalence when there is a rich published literature for the treatment of specific medical conditions. For the study of acute treatment of ischemic stroke, previous efforts have been used as a meta-analysis of this literature, but not by this method.

There are five randomized trials demonstrating the benefit of revascularization after ischemic stroke that form the basis of such analyses. Goyal et al. (2015) presented the results of the

ESCAPE trial, Berkhemer et al. (2015) presented the MRCLEAN trial, Joyin et al. (2015) presented the results of the REVASCAT trial, Campbell et al. (2015) presented the results of the EXTEND 1A trial, and Saver et al. (2015) presented the results of the SWIFT PRIME trial. The computations of the method are described below.

If C is the number of study sites or geographic locations (whichever demonstrates non-homogeneity in the response) then the weighted success rate will be computed in the following way:

$$W_c = 1/s_c^2$$

where W_c is the weight for site or geographic location c and s_c^2 is the variance of the estimate of success from site or geographic location c.

Y_c is the estimate of the rate of success from site or geographic location c. The inverse variance weighted mean success rate is given by

$$\bar{Y} = \frac{\sum_{c=1}^{C} W_c Y_c}{\sum_{c=1}^{C} W_c}.$$

The standard error of the mean is given by

$$SE(\bar{Y}) = \left(\sum_{c=1}^{C} W_c \right)^{-1/2}.$$

The two-sided 95% confidence limits can be obtained on $\bar{Y}$ by the following formula

$$\bar{Y} \pm z_\alpha * SE(\bar{Y}).$$

To determine if the rates are homogeneous across study groups compute Q as follows

$$Q = \sum_{c=1}^{C} W_c \left(Y_c - \bar{Y} \right)^2$$

If Q > C-1, then an adjustment for heterogeneity in rates among groups is needed. The following three quantities are needed for this adjustment:

$$\bar{W} = \frac{\sum_{c=1}^{C} W_c}{C}$$

$$S_W^2 = \frac{1}{C-1} \left(\sum_{c=1}^{C} W_c^2 - C\bar{W}^2 \right), \text{ and}$$

$$U = (C-1)\left(\overline{W} - \frac{S_W^2}{C\overline{W}}\right).$$

The inter-study variation in effect size, D, is computed as follows

D=0 if Q≤C-1

And

$$D = \frac{Q-(C-1)}{U} \text{ if Q>C-1.}$$

An adjusted weighting factor is computed as

$$W_c^* = \frac{1}{D + W_c^{-1}}.$$

The revised mean study group estimate of success is given by

$$\overline{Y}^* = \frac{\sum_{c=1}^{C} W_c^* Y_c}{\sum_{c=1}^{C} W_c^*}.$$

The standard error of this estimate is given by

$$SE\left(\overline{Y}^*\right) = \left(\sum_{c=1}^{C} W_c^*\right)^{-1/2}.$$

Confidence limits are computed as follows if there is heterogeneity among the rates.

$$\bar{Y}^* \pm z_\alpha * SE(\bar{Y}^*).$$

The five studies were combined by this method in the tables below. The first table provides the estimate unadjusted for heterogeneity and the second table adjusts the estimate for heterogeneity based on the value of Q.

Only the test arm of the five trials are provided below with success being defined as having a 90-day modified Rankin Score of 0 to 2.

Table 1 Unadjusted Mean and 95% Confidence Limits on the Literature Rates

Study	N	X	Y_C	VAR[a]	W_C	$W_C Y_C$	W_C^2
SWIFT PRIME	98	59	0.6020	0.0024448	409.036071	246.25641	167310.508
ESCAPE	120	64	0.5333	0.0020741	482.142857	257.142857	232461.735
REVASCAT	103	45	0.4369	0.0023885	418.669349	182.913793	175284.024
EXTEND 1A	35	25	0.7143	0.0058309	171.5	122.5	29412.25
MRCLEAN	233	76	0.3262	0.0009433	1060.11876	345.789809	1123851.78
				SUM	1154.60287	2541.46703	1728320.29
					$\bar{Y}$	LCL	UCL
				C=5	0.4543	0.4154	0.4932

[a]The VAR term in the table is actually the standard error of the Y_C.

In the table below, the test of heterogeneity is computed and the adjustment if Q>C-1.

Table 2 Adjusted Mean and 95% Confidence Limits on the Literature Rates

Study	Y_C	$\bar{Y}$	$Y_C-\bar{Y}$	$(Y_C-\bar{Y})^2$	$W_C (Y_C-\bar{Y})^2$	W_C^*	$W_C^* Y_C^*$
SWIFT PRIME	0.6020	0.4543	0.1477	0.02182568	8.9275	44.7338	26.9316
ESCAPE	0.5333	0.4543	0.0790	0.00624537	3.0112	45.4881	24.2603
REVASCAT	0.4369	0.4543	-0.0174	0.00030319	0.1269	44.8467	19.5932
EXTEND 1A	0.7143	0.4543	0.2600	0.06758963	11.5916	38.8492	27.7494
MRCLEAN	0.3262	0.4543	-0.1281	0.01641612	17.4030	47.9548	15.6419
				SUM Q=	41.0602	221.8726	114.1764
$\bar{W}$=	508.29341						
S_W^2=	109127.34			D_1=	0		
U=	1861.4188			D_2=	0.01990968		
				$\bar{Y}^*$	$SE(\bar{Y}^*)$	LCL	UCL
				0.5146	0.0671	0.3830	0.6462

Since Q>C-1, an adjustment was made to the mean success rate and the between study standard error has increased to 0.0671. This demonstrates that the upper and lower limits are 0.5146 ±0.1315 (1.96*0.0671). The variability between and within the five studies is 0.13 (13%) and a margin of equivalence that size or smaller would be appropriate. The non-inferiority margin for this study will be set at -12.5%.

This same exercise was followed for SICH, eTICI 2b50 or greater flow, and mortality. The details are presented in Section 14 under Additional Considerations. In summary, the non-inferiority margins for SICH, eTICI 2b50 or greater flow in the target vessel post-procedure, and mortality will be set at 5%, -12.1%, and 10%, respectively.

4.4. Sample Size Justification

The objective of this trial is to demonstrate similar performance after treatment with the pRESET device compared to the expected proportion of good outcomes at 90 days in the Solitaire arm. The expected proportion of good outcomes in the pRESET arm was estimated based on earlier results with Solitaire. A -12.5% non-inferiority margin (NIM) will be used to examine the lower bound of the 1-sided 95% exact binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with a 90 day mRS of 0-2. The null hypothesis and alternative hypothesis is presented below.

H_o: pRESET – Solitaire ≤ -12.5%
H_a: pRESET – Solitaire > -12.5%

If the lower bound of the 1-sided 95% exact binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with a 90 day mRS of 0-2 is greater than -12.5%, then non-inferiority will be established.

The planning estimates for the PROST study considered the lower bound of the 2-sided 95% (asymptotic) confidence interval from the SWIFT PRIME study for estimation (50.5%). Sample size estimates were prepared for this parallel design study assuming a non-inferiority margin of -12.5% (pRESET successes [%] minus Solitaire successes [%]). Under the alternative hypothesis, non-inferiority would be claimed if the lower bound of the 1-sided 95% confidence interval of the difference is less than the non-inferiority margin of -12.5%.

For planning purposes, the estimated effectiveness of the Solitaire device was based on a previously published meta-analysis of 5 randomized trials in which the effectiveness of endovascular thrombectomy over standard medical care was shown. This study was referred to as the HERMES collaboration. Of the 633 included participants that received thrombectomy, 46.0% (291) achieved a good outcome based on an mRS score ≤ 2 at 90 days. The expected effectiveness of the pRESET thrombectomy device was based on the SWIFT PRIME study where 98 patients were treated with the Solitaire FR (Flow Restoration) or Solitaire 2 device. In total, 59 out of the total 98 patients who were treated achieved an mRS score less than or equal to 2. As the reported 60% patients with good outcome in the SWIFT PRIME study might be an overestimation of the actual result, the lower bound of the 95% CI was calculated based on a normal approximation. The construction of a confidence interval around the estimate of SWIFT PRIME yielded a 95% CI of [50.5% - 69.9%]. Assuming 46% of the Solitaire patients and 50.5% of the pRESET patients have an mRS score ≤ 2 at 90 days, 214 total patients will be required. If the gap narrows between the 2 randomized groups to 49.5% (Solitaire) and 50.5% (pRESET), 340 total patients will be required (type 1 error rate of 5%, power of 80%).

Estimates were also prepared for the secondary endpoints. For the primary safety endpoint (sICH within 24 hours (-8/+12 hours) after the study procedure), the incidence of sICH is not expected to exceed 2% in either arm of the study. The total sample size required for 80% power, a type 1 error rate of 5%, and a non-inferiority margin of 5% is 290 patients.

For the proportion of patients with eTICI 2b50 or greater flow (single pass and after a maximum of 3 passes), the proportion of patients with eTICI 2b50 or greater flow incidence of SICH is expected to be ~74% in both arms of the study. The total sample size required for 80% power, a type 1 error rate of 5%, and a non-inferiority margin of 12.2% is 326 patients.

Ninety days following the index stroke, mortality is not expected to be exceed ~13.8% in both arms of the study. The total sample size required for 80% power, a type 1 error rate of 5%, and a non-inferiority margin of 10% is 308 patients.

4.5. Estimated Duration of Patient Participation and Follow-up

The duration of this study for each patient will be a maximum of 120 days, beginning screening immediately (assumed to be immediately prior to the procedure). The table presented below provides the relative study day with the targeted study day for evaluations and expanded time windows for evaluations that may occur outside of the targeted time window. Note the expanded

time windows are intended to include all recorded observations. If 2 observations are obtained equal distant to the relative study day, the earlier observations will be used with all observations presented in the listings.

Table 3. Targeted Study Day for Evaluation

Visit and Relative Study Day	Targeted Study Day and Time Window	Expanded Time Window
Screening	Assumed to be conducted shortly before the procedure	Assumed to be conducted shortly before the procedure
Procedure	1	1
24-hour (16 to 36 hours, inclusive) post-procedure	2	2 to 3
7 days (5 to 7 days, inclusive)	5 to 7	4 to 15
30 days (21 to 37 days, inclusive)	21 to 37	16 to 59
90 days (75 to 105 days, inclusive)	75 to 105	60 to 120

4.6. Study Randomization and Blinding

The treatment team will obtain a randomization assignment using a web-based randomization system. Randomization (1:1 ratio) will be stratified by 5 factors using a permuted block randomization scheme:

- Age: ≥65 and <65
- Site of occlusion: ICA, MCA and BA
- Baseline/Enrollment NIHSS score: <17 and ≥17
- Prior IV t-PA usage: Yes and No
- Time to symptom onset: ≥4 hours and <4 hours

Time from the first observed symptoms of a stroke to the time the patient signs the informed consent will be dichotomized as ≥4 hours and <4 hours. If the date and time is not available, the date and time of randomization will be used. This randomized trial will ensure that the assessing study team along with the Core Laboratory readers are blinded to the treatment assignment. Due to the nature of the treatment, and patient access to records, the treatment team and the patient are not required to be blinded.

5. SCHEDULE OF ASSESSMENTS

The schedule of assessments is presented from Section 7.18 of the protocol.

	Screening	Procedure	24-hour post-procedure	7 days	30 days	90 days
Timeframe / Assessment	0 hrs	Index	16-36 hrs	5-7 days	21-37 days	75-105 days
Eligibility criteria	X					
Demographics and medical history	X					
NIH Stroke Scale	X		X	X	X*	X*
Prestroke mRS	X					
mRS	X			X	X	X
MR or CT Imaging	X		X	X*		
Catheter angiogram	X	X				
ASPECTS (0-8 hr symptom onset)	X					
Core infarct size	X					
MR or CT Angiography	X*			X*		
Procedure characteristics		X				
Medications/AE's	X	X	X	X	X	X
Barthel Index	X			X	X	X

* Optional assessments:
- Imaging based on Standard of Care / Institutional Protocol
- NIH Stroke Scale not required if follow-up is completed over the phone

6. ANALYSIS POPULATIONS

The results from this study will be presented using 3 populations:

1. **Primary Analysis Population:** Intent-to-Treat (ITT) Population

   All enrolled patients who have signed the ICF, meet the eligibility criteria, and are randomized in the study will be analyzed irrespective of the treatment actually delivered. The intention-to-treat principle defines that every patient randomized to the clinical study should enter the primary analysis. Accordingly, patients who drop out prematurely, are non-compliant to the study treatment, or even take the wrong study treatment, are included in the primary analysis within the respective treatment group they have been assigned to at randomization. The ITT population will also serve as the Safety population.

2. **Secondary Analysis Population:** Per-Protocol (PP) Population

   All enrolled patients who met all eligibility criteria and who had the primary endpoint assessments according to the protocol (i.e. underwent treatment with the pRESET thrombectomy device or Solitaire device & received a clinical 90 days post-procedure event review for the efficacy endpoint analysis). In the PP protocol analysis patients will be analyzed and included in the group in which they were randomized.

   All major protocol deviations (i.e., deviation from subject inclusion and exclusion criteria, subject informed consent procedures or unauthorized device use) will be reviewed and patients with deviations from subject informed consent procedures or unauthorized device use that affect data integrity will also be listed for exclusion from the PP Population.

   A final list of all subjects excluded from the PP Population will be finalized prior to database lock.

3. **Tertiary Analysis Population:** As-Treated (AT) Population

   All enrolled patients who actually received treatment will be analyzed according to the treatment these patients actually received irrespectively of the treatment they were assigned to.

7. ANALYSIS CONVENTIONS AND MODEL DISPLAYS

Post-text tables and Listings will be prepared in accordance with the current ICH Guidelines. The header of each table and Listing will include the sponsor's name and the study number. The information and explanatory notes to be provided in the "footer" or bottom of each table and Listing will include the following information:

1. Date and time of output generation.
2. SAS® program name, including the path that generates the output.
3. Any other output specific details that require further elaboration.

In general, tables will be formatted with a column displaying findings for all patients combined. Row entries in tables are made only if data exist for at least one patient (*i.e.*, a row with all zeros will not appear). The only exception to this rule applies to tables that list the termination status of patients (*e.g.*, reasons for not completing the study). In this case, zeros will appear for study termination reasons that no patient satisfied. The summary tables clearly indicate the number of patients to which the data apply and unknown or not performed are distinguished from missing data. Tables, Listings, and figures will provide the units of measurement, unless not applicable.

Results recorded at single times during the study will be presented using the *Level 1* display for the Safety Population; the example structure is presented below.

- Patients randomized to the Solitaire device (Treatment Group 1),
- Patients randomized to the pRESET Group (Treatment Group 2), and
- All randomized patients.

Parameter and Statistic	Patients Randomized to pRESET N=xxx	Patients Randomized to Solitaire N=xxx	All Randomized Patients N=xxx
Age ● n ● Mean ● Standard Deviation ● Median ● Minimum, Maximum			
Gender ● Male (n [%]) ● Female (n [%])			

The *Level 2* display will be used for summarizing the incidence of AEs during each of the study phases. An example of the layout for AEs by severity is presented below.

System Organ Class Preferred Term	Patients Randomized to pRESET N=xxx	Patients Randomized to Solitaire N=xxx	All Randomized Patients N=xxx
SOC PT			

The *Level 3* display will be used for summarizing the parameters recorded multiple times during the follow-up visits. An example of the layout is presented below; rows will be repeated for all visits where a measurement is recorded using the expanded time windows.

Statistic	Observation Time	Patients Randomized to pRESET N=xxx	Patients Randomized to Solitaire N=xxx	All Randomized Patients N=xxx
n Mean (SD) Median Minimum, Maximum	Baseline			
n Mean (SD) Median Minimum, Maximum	Post-Dose			
n Mean (SD) Median Minimum, Maximum	Change from Baseline			

SD: Standard deviation

The Level 3 displays will report the paired results for the change from the baseline for the follow-up and final study visit. For example, if 18 patients complete the baseline evaluation and 16 patients complete follow-up, the difference (Follow-up minus Baseline) will contain 16 patients.

Supportive individual patient data Listings will be sorted and presented by patient number and visit date, if applicable. Listings will also include the number of days relative to the initial study treatment.

Specific algorithms are discussed for imputing missing or partially missing data, if deemed appropriate, under specific data topics. Imputed or derived data will be flagged in the individual patient data Listings. Imputed data will not be incorporated into any raw or primary datasets. The imputed data will be retained in the derived / analysis datasets.

The total duration for a patient *on-study* will be calculated as the difference between the date of informed consent and the last day of observation plus 1 day. All calculations for defining the duration on-study will follow the algorithm DURATION = [STUDY COMPLETION OR

WITHDRAW DATE – INFORMED CONSENT DATE + 1]. Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in patient listings. Demographic and safety summary statistics will be presented for all patients in the Safety Population. Data from patients excluded from an analysis population will be included in the data listings, but not in the summaries.

For changes from baseline (pre-procedure), only changes from baseline (pre-procedure) to the defined post-procedure time point will be shown in the listings and tabulations. Listings will include all assessments (including repeated and unscheduled measurements) in chronological order with the scheduled measurements. Unscheduled and/or repeated measurements (unless used as the baseline measurement) will not be included in the tables. If any baseline (pre-procedure) value is missing, the change from baseline will not be calculated.

Both observed and imputed results will be presented

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- Summary statistics will consist of the count, percentage, and exact 95% binomial confidence intervals at each level for categorical variables, and the sample size (n) mean, median, standard deviation (SD), minimum, and maximum values for continuous variables.

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

- The number and percentage of responses will be presented in the form XX (XX.X%).

- All probability values will be rounded to four decimal places. All p-values that round to 0.0000 will be presented as ‘<0.0001’ and p-values that round to 1.0000 will be presented as ‘>0.9999’. P-values <0.05 will be considered to be statistically significant.

- All summary tables will include the analysis population sample size (i.e., number of patients with values for the analysis).

- Study Day 1 is defined as the day the patient receives their initial study treatment. All *study days* are determined relative to the day of the initial treatment.

- Baseline values will be defined as those values recorded closest to, but prior to, the procedure.

- Change from baseline will be calculated as follows:
    - Change = Post-baseline value – baseline value.

- Date variables will be formatted as DDMMMYYYY for presentation.

- Tables, figures, and Listings will be presented in landscape orientation.

- SAS® Version 9.4 will be the statistical software package used for all data analyses.

- All data from this study will be presented in Listings. All Listings will be sorted by clinical site, patient number, and visit date, as applicable.

Table and Listing numbering will follow ICH guidelines for post-text table and Listing numbering.

7.1. Adjustments for Covariates

The analyses of the primary and secondary endpoints will be conducted with and without the adjustment for covariates determined to be significantly different at baseline. The initial set of analyses conducted as the study results of record will not be adjusted for any categorical factors found to be significantly different between the randomized treatment groups at baseline.

The randomization scheme is intended to control for the 5 factors through stratification:

- Age: ≥65 and <65
- Site of occlusion: ICA, MCA and BA
- Baseline/Enrollment NIHSS score: <17 and ≥17
- Prior IV t-PA usage: Yes and No
- Time to symptom onset: ≥4 hours and <4 hours

If one or more factors are found to be significant ($p<0.05$) between the randomized treatment groups at baseline, the factor will be retained in the adjusted analysis of each of the primary and secondary endpoints. The examination of each baseline factor will be performed using a Fisher's Exact test for categorical variables and a 1-factor (treatment) analysis of variance test for continuous variables, as described in section 8.

7.2. Addressing Missing Data in the Analyses

Missing data, which in this instance is defined as data that was not entered into the EDC system or the Core Lab file for analysis, may have an impact upon the interpretation of the trial data. For patients who died on study that do not have an mRS score recorded as a 6 on or after the time of their death will have a 6 imputed as their score.

The primary presentation of the results for the primary and secondary endpoints using the ITT population will be based on the observed data with multiple imputation for missing endpoint data using SAS PROC MI. The exploratory endpoints will be analyzed using the observed data. This procedure uses an iterative modeling approach to generate estimates for patients who withdraw prematurely, or the data is just not recorded, incorporating multivariate imputation by fully conditional specification (FCS) methods. The discriminant function method will be used for classification variables. With the function method of classification, the missing values will be imputed sequentially in the following order:

- Age: ≥65 and <65
- Site of occlusion: ICA, MCA and BA
- Baseline/Enrollment NIHSS score (<17 / ≥17)

- Prior IV t-PA usage (Yes / No)
- Time to symptom onset (≥4 hours / <4 hours)

Each missing score will be imputed ten times to generate ten imputed complete datasets based on the Markov Chain Monte Carlo (MCMC) method with age, occlusion site, NIHSS score (<17 / ≥17), prior IV t-PA usage (yes / no), and time to symptom onset (≥4 hours / <4 hours) entered into the model following this sequential order. The imputed score will be rounded to the first decimal point for continuous variables. Proc MIANALYZE will be used to combine the imputed datasets to render an analysis of the binary outcomes for the results for the primary effectiveness and safety endpoints and the first 3 of the 4 secondary endpoints. The fourth secondary endpoint analysis will follow the method outlined to calculate the odds ratio with the imputed dataset.

Additional sensitivity analyses will also be conducted as a secondary examination of the primary analysis using the last observation recorded following the procedure observation carried forward. A tipping point analysis will also be conducted. (Reference: Table 14.4.1.8 entitled Modified Rankin Scale (mRS) Scores 0-2 Results by Randomized Group Based on the Last Recorded mRS Score (Sensitivity Analysis) and Table 14.4.1.9 entitled Tipping Point Analysis for the Modified Rankin Scale (mRS) Scores 0-2 Results by Randomized Group)

If a patient did not have solicited adverse events of special interest [incidence by type of event] prior to withdrawing prematurely from the study, the patient will be considered as not having experienced the event.

Handling of Missing or Partial Medication/Intervention Dates/First and Last Recorded Neurological event

A pre-study medication or procedure is defined as any medication taken or intervention performed during the pre-procedural phase with a start-date prior to the date of study procedure. If the date of the study procedure is not recorded, the date of informed consent will be used.

The date of the first recorded neurological event is the patient-reported date of their initial event, including event recorded well in advance of the pre-procedural phase of the study. The date of the last recorded neurological event is the patient-reported date of their most recent event prior to the study procedure. The rules described in this section for post-procedural medications and procedures will be applied to missing or incomplete dates for the first and last reported neurological event.

Post-procedural medications or procedures are defined as any medication or intervention besides the study procedure with a start-date on or after the study procedure through the follow-up phase of the study. Additionally, any medications or interventions continued from pre-treatment phase will be considered as pre-procedural unless the dose or intensity of the procedure increased.

Handling of Missing Start-dates for Interventions

For the remainder of this section, an intervention refers to any intervention other than study procedure.

Rules for imputing a full date for interventions with incomplete or missing start-dates are addressed below. In the unusual case that the month portion of an intervention start-date is missing but the day portion is not missing, the day portion of the intervention will be assumed to be missing. Likewise, in the case where the year portion of an intervention start-date is missing but the month

and/or day portion is not missing, the month and/or day portion of the intervention start-date will be assumed to be missing. All missing portion(s) of the intervention starting dates will be handled using the same rules:

- In the event that the day portion (and only the day portion) of the intervention start-date is missing:
    - If the intervention started in the same month and year as the study procedure, the intervention start-date will be assumed to be the date of the study procedure (*i.e.*, Study Day 1);
    - Otherwise, the intervention start-date will be assumed to be the 15th day of the given month and year, *e.g.*, XX–DEC-2005 → 15-DEC-2005 where XX represents an unknown value.
- In the event that the day and month portion (and only the day and month portion) of the intervention start-date are missing:
    - If the intervention started in the same year as the study procedure, the intervention start-date will be assumed to be the date of the study procedure (*i.e.*, Study Day 1);
    - Otherwise, the intervention start-date will be treated as July 1st of the given year, *e.g.*, XX-XXX-2005 → 1-JUL-2005.
- In the event that the day, month, and year portion of the intervention start-date are missing, the start-date of the intervention will be assumed to be the date of the study procedure (*i.e.*, Study Day 1).

Note: With the exception of the following special cases, this conservative scheme ensures that an intervention with a partially or completely missing start-date will be treated as post-procedural.

Special Cases on Missing Intervention Start-dates

- Using the above rules for the handling of missing intervention start-dates, if the assumed intervention start-date:
    - is later than the reported intervention stop-date, the assumed intervention start-date will be reset and assumed to be the intervention stop-date.
- If, based on the above rules, it cannot be determined whether the intervention was taken prior to the study procedure, it will be assumed to be post-procedural.

Several Examples of Handling Missing Intervention Start-Dates

Assume that the date of the study procedure for a patient is 04-FEB-2005 and the Screening Date is 18-JUL-2004

- Example: The day portion (and only the day portion) of the intervention start-date is missing:
    - If the intervention start-date is XX-DEC-2004 then the assumed intervention start-date is 15-DEC-2004.

- If the intervention start-date is XX-FEB-2005 then the assumed intervention start-date is 04-FEB-2005, as the intervention started in the same month and year as the study procedure.

- Example: The day and month portion (and only the day and month portion) of the intervention start-date are missing
  - If the intervention start-date is XX-XXX-2004:
    - then the assumed intervention start-date is 15-JUN-2004 using the rules;
    - but this is a special case since the assumed start-date of 15-JUN-2004 is before the patient's screening date 18-JUL-2004. Therefore the assumed intervention start-date will be reset and assumed to be 18-JUL-2004.
  - If the intervention start-date is XX-XXX-2005 then the assumed intervention date is 04-FEB-2005, as the intervention started in the same year as the date of the study procedure.

- Example: The day, month, and year portion of the intervention start-date are missing (*i.e.*, if the intervention start-date is XX-XXX-XXXX), then the assumed intervention start-date is 04-FEB-2005.

7.3. Multiple Comparison/Multiplicity

No adjustment for multiplicity will be applied to the type 1 error rate in the analysis of the efficacy endpoint results from this study. Alpha inflation will be protected by the hierarchical stepdown approach used in the order of conducting the testing strategy. The order for analysis of the 4 secondary endpoints using the step down approach to control for inflation of the type 1 error rate will be as follows: Secondary endpoint 2, 1, 3 and 4.

Testing will follow the sequential order of the secondary endpoints (2, 1, 3 and 4), and the secondary endpoints will only be evaluated statistically if the primary endpoint is non-inferior to the Solitaire device. All planned comparisons will be conducted; accepting the results at face value will be dependent on the hierarchical testing strategy to prevent inflation of the type 1 error rate.

7.4. Examination of Subgroups

Depending on the significance of the individual endpoints, the results will be examined by individual subgroups. Results may be evaluated relative to a specific characteristic or factor. At the time of preparing the SAP, the following sub-groups have been identified:

- Age >80 years at the time of the procedure
- Age >70 years at the time of the procedure
- Age ≥65 years at the time of the procedure
- Site of occlusion: ICA
- Site of occlusion: MCA
- Site of occlusion: BA
- Baseline/Enrollment NIHSS score: <17
- Baseline/Enrollment NIHSS score: ≥17
- Prior IV t-PA usage

- No prior IV t-PA usage
- Time to symptom onset: ≥4 hours
- Time to symptom onset: <4 hours

8. STATISTICAL ANALYSIS

8.1. Patient Accounting and Study Disposition

A complete accounting of patient participation in the study will be presented in Table 14.1.1 entitled *Patient Accounting and Final Study Disposition*. The purpose of this table is to provide an accounting of patients from their entrance into the study through the final visit and to account for the evaluations of patients in the major analyses of effectiveness and safety, including reasons for early study termination. The table will display the number and percentage of patients that were:

- Randomized
- Underwent the Study Procedure
- Contacted for the 30-Day Follow-up Evaluation
- Completed the 30-Day Follow-up Evaluation (based on the visit windows)
- Contacted for the 90-Day Follow-up Evaluation (based on the visit windows)
- Completed the 90-Day Follow-up Evaluation (based on the visit windows)
- Discontinued from the Study
    - Withdrew Consent
    - Died
    - Other (list exact reason)

Table 14.1.1.1 entitled *Patient Accounting and Final Study Disposition by Investigational Site* will follow a similar format and tabulation used in Table 14.1.1, however this table will be presented by investigation site. The sites will also be identified as within the USA or outside of the USA.

Table 14.1.1.2 entitled *Reasons Patients Did Not Undergo the Study Procedure* will contain a tabulation of the number of patients classified by the individual reason. This table only contains the patient counts and is sorted alphabetically by the reason for not undergoing the study procedure.

Listing 16.1 entitled *Patient Disposition* supports Tables 14.1.1 through 14.1.1.2. This listing will be sorted by patient number and will include the reason for withdraw for all patients who discontinue prematurely.

Listing 16.2.1 entitled *Inclusion Criteria* displays the data from the Inclusion Criteria case report form. The data will be displayed for each patient and for each inclusion criterion. The listing will be sorted by patient number.

Listing 16.2.2 entitled *Exclusion Criteria* displays the data from the Exclusion Criteria case report form. The data will be displayed for each patient and for each exclusion criterion. The listing will be sorted by patient number.

8.2. Baseline Demographic Factors and Patient Characteristics Recorded at Screening

Results will be presented for each of the following 3 categories

● Patients randomized to the Solitaire device (Treatment Group 1),

● Patients randomized to the pRESET Group (Treatment Group 2), and
● All randomized patients.

Results will be presented in Table 14.1.2 entitled *Summary of Patient Demographics and Characteristics* (All Screened Patients). The Level 1 table layout will be used to present these results. This table summarizes the patient population with respect to gender, age in years at the time of entry into the study, height (cm), weight (kgs.), BMI, blood pressure and pulse rate at the time of screening. Factors found to be significant between the 2 treatment groups will be considered for inclusion in the sensitivity analyses for the primary effectiveness and safety endpoints. Table 14.1.2.1 entitled *Summary of Patient Demographics and Characteristics by Clinical Site* (All Screened Patients) will examine the differences across sites by treatment assignment.

This tables summarize the patient population with respect to age at entry into the study, gender, ethnicity, and race. Age will be calculated as:

[Date of Informed Consent – Date of Birth] / 365.25 rounded down to the nearest integer.

Age will be reported in years. Age, height, weight, BMI, blood pressure and pulse rate will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, range (*i.e.*, minimum and maximum values) and compared between the randomized treatment assignments using a one-factor (randomized treatment assignment) analysis of variance test. Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics.

The number and percent of patients ≥65 and <65, >70 and ≤70, and ≤80 and >80 years of age at the time of enrollment will also be presented. Results will be presented based on the number of patients in each category using counts and percentages. The proportion of patients in each mutually-exclusive category will be compared between the randomized device groups using a two-tailed Fisher's exact test. Gender will also be compared between the randomized device groups using a two-tailed Fisher's exact test.

The supportive data for Table 14.1.2 will be presented in Listing 16.4.1 entitled *Patient Demographics*. This listing will be sorted by clinical site and patient number.

8.3. Laboratory Results Recorded at Screening

Results will be presented for each of the following 3 categories

● Patients randomized to the Solitaire device (Treatment Group 1),
● Patients randomized to the pRESET Group (Treatment Group 2), and
● All randomized patients

Results will be presented in Table 14.1.3 entitled *Summary of Patient Laboratory Results Recorded During Screening* (All Screened Patients). The Level 1 table layout will be used to present these results. This table summarizes each laboratory parameter using descriptive statistics: n, arithmetic mean, standard deviation, median, range (*i.e.*, minimum and maximum values) and compared

between the randomized treatment groups using a one-factor (randomized treatment assignment) analysis of variance test. Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics.

The supportive data for Table 14.1.3 will be presented in Listing 16.5.1 entitled *Laboratory Results*. In addition to the parameters listed below, the results of the pregnancy test will also be presented. This listing will be sorted by clinical site and patient number. A list of the individual parameters is listed below.

Blood

- INR
- Platelet Count
- Glucose
- PTT
- GFR
- White blood cell count
- Red blood cell count
- hemoglobin
- Hematocrit
- Calcium
- Creatinine
- Total cholesterol
- Potassium

Urine

- Leukocytes
- Nitrite
- Urobilinogen
- Protein
- pH
- Hemoglobin
- Urine specific gravity
- Ketone bodies
- Bilirubin
- Glucose

8.4. Summary of Symptoms at Stroke Onset

All enrolled patients will be included in Table 14.1.4 entitled *Summary of Solicited Stroke Symptoms at the Time of Onset Recorded at Screening*. Results will be presented for each of the following 3 groups

● Patients randomized to the Solitaire device (Treatment Group 1),
● Patients randomized to the pRESET Group (Treatment Group 2), and
● All randomized patients

The solicited symptoms are as follows:

- Weakness of face? (yes or no) and the side
- Weakness of arms? (yes or no) and the side
- Weakness of legs? (yes or no) and the side
- Problem with Vision? (yes or no) and the side
- Confusion, problem with speaking or understanding? (yes or no)
- Vertigo, difficulty with swallowing? (yes or no)
- Headache? (yes or no)
- Others? (yes or no)

The supportive data for Table 14.1.4 will be presented in Listing 16.4.2 entitled *Symptoms at the Time of Stoke Onset*. This listing will be sorted by clinical site and patient number.

8.5. Administration of t-PA Recorded at Screening

All enrolled patients will be included in Table 14.1.5 entitled *Summary of t-PA Administration Recorded at Screening*. Results will be presented for each of the following 3 groups

● Patients randomized to the Solitaire device (Treatment Group 1),
● Patients randomized to the pRESET Group (Treatment Group 2), and
● All randomized patients

From the date and time of stroke onset, the time to the administration of IV t-PA will be reported in hours. The time to treatment (minutes) and the dose of t-PA administered will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, range (*i.e.*, minimum and maximum values) and compared between the randomized treatment assignments using a one-factor (randomized treatment assignment) analysis of variance test. Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics.

The supportive data for Table 14.1.5 will be presented in Listing 16.4.3 entitled *Treatment with t-PA*. This listing will be sorted by clinical site and patient number.

8.6. Neurologic Status Recorded at Screening

All enrolled patients will be included in Table 14.1.6 entitled *Summary of Neurologic Status Recorded at Screening*. Results will be presented for each of the following 3 groups

● Patients randomized to the Solitaire device (Treatment Group 1),
● Patients randomized to the pRESET Group (Treatment Group 2), and
● All randomized patients

The supportive data for Table 14.1.6 will be presented in Listing 16.6.1 entitled *Neurologic Status*. This listing will be sorted by clinical site and patient number.

The NIHSS at admission to the study hospital will be summarized using descriptive statistics. The scores will be compared between the randomized treatment groups using a one-factor (randomized treatment assignment) mixed model. **Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics.** The SAS code for this analysis is presented below.

```
proc mixed data=ADNSYMP_001;
class COHORT_N;
model NIHADM = COHORT_N;
lsmeans COHORT_N;
run;
```

The mRS before the onset of the stroke and at admission to the study hospital will be summarized using counts and percentages for each category from 0 to 6. A generalized linear model (Proc Genmod) will be used to compare the distribution of scores between the randomized treatment groups specifying the distribution as multinomial. Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics. The SAS code for this analysis is presented below.

```
proc genmod data=ADNSYMP_001 descending;
class COHORT_N ;
model MRSADM = COHORT_N  / dist=multinomial link=cumlogit type3;
```

A secondary examination of the mRS scores will be conducted to determine if there are differences among the stratification variables. Results will be presented in Table 14.1.7 entitled *Summary of the Modeling Based on the Pre-Procedure Modified Rankin Scale (mRS) Scores Results* (ITT Population). Results will be presented using the ITT population without imputation. A random-effects generalized linear model for independent data by maximum likelihood that allows for patient-specific (conditional) and population-averaged (marginal) inference (PROC GLIMMIX) will also be generated, incorporating predictive factors and stratification variables specified in the randomization as covariates:

- Age: ≥65 and <65 [AGE_CAT]
- Site of occlusion: ICA, MCA and BA [OCC_SITE]
- Baseline (Screening) NIHSS score: <17 and ≥17 [NIHSS]
- Prior IV t-PA usage: Yes and No [T-PA]
- Time to symptom onset: ≥4 hours and <4 hours [T_SYMP]

Although the patient has not undergone treatment at this juncture, the randomization assignment will be added to the model. The example code for conducting this analysis is presented below:

```
ODS OUTPUT TESTS3 = TESTS_OB_TIME_2;
proc glimmix data=ADEFF_OB_TIME_2 method=laplace;
   class SUBJID TRTN RANDOM_LOC RANDOM_AGE RANDOM_NIHSS RANDOM_IVTPA
RANDOM_ONSET;
   model SCORE = TRTN RANDOM_LOC RANDOM_AGE RANDOM_NIHSS RANDOM_IVTPA
RANDOM_ONSET / dist=multinomial link=cumlogit ddfm=residual solution cl or
alpha = 0.1;
```

```
   random SUBJID / solution;
   CONTRAST "PRESET VS. SOLITAIRE" TRTN -1 1 / EST;
   ESTIMATE  "PRESET VS. SOLITAIRE" TRTN -1 1 / CL;
run;
ODS OUTPUT CLOSE;
```

The factors listed below will be used in the model.

- Age: ≥65 and <65 [RANDOM_AGE]
- Site of occlusion: ICA, MCA and BA [RANDOM_LOC]
- Baseline/Enrollment NIHSS score: <17 and ≥17 [RANDOM_NIHSS]
- Prior IV t-PA usage: Yes and No [RANDOM_IVTPA]
- Time to symptom onset: ≥4 hours and <4 hours [RANDOM_ONSET]
- pRESET (1) and Solitare (2) [TRTN]

An example of how this information from the analysis will be displayed is presented below.

Modified Rankin Score	Patients Randomized to pRESET N=xxx	Patients Randomized to Solitaire N=xxx
mRS = 0	n (%)	n (%)
mRS = 1	n (%)	n (%)
mRS = 2	n (%)	n (%)
mRS = 3	n (%)	n (%)
mRS = 4	n (%)	n (%)
mRS = 5	n (%)	n (%)
mRS = 6	n (%)	n (%)

Adjusted Odds Ratio (95% CI) for Treatment Effect	1.000 (0.0000, 10.0000)
P-value for Age: ≥65 and <65	0.0000
P-value for Site of occlusion: ICA, MCA and BA	0.0000
P-value for NIHSS score: <17 and ≥17	0.0000
P-value for Prior IV t-PA usage	0.0000
P-value for Time to symptom onset: ≥4 hours and <4 hours)	0.0000
P-value for Study Treatment	0.0000

This analysis will be repeated dichotomizing the mRS before the onset of the stroke and at admission to the study hospital: 0 to 2 [0=No symptoms at all, 1=No significant disability despite symptoms; able to carry out all usual duties and activities, and 2=Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance] and 3 through 6 [3=Moderate disability; requiring some help, but able to walk without assistance, 4=Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance, 5=Severe disability; bedridden, incontinent and requiring constant nursing care and attention, and 6=Dead]

Although the patient has not undergone treatment at this juncture, the randomization assignment will again be added to the model. **Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics.** The example code for conducting this analysis is presented below:

```
proc glimmix data=ADEFF_OB_TIME_1 method=laplace;
   class SUBJID TRTN RANDOM_LOC RANDOM_AGE RANDOM_NIHSS RANDOM_IVTPA
RANDOM_ONSET;
   model SCORE = TRTN RANDOM_LOC RANDOM_AGE RANDOM_NIHSS RANDOM_IVTPA
RANDOM_ONSET / dist=multinomial link=cumlogit ddfm=residual solution cl or
alpha = 0.1;
   random SUBJID / solution;
   CONTRAST "PRESET VS. SOLITAIRE" TRTN -1 1 / EST;
   ESTIMATE  "PRESET VS. SOLITAIRE" TRTN -1 1 / CL;
run;
```

All enrolled and randomized patients will be included in Table 14.1.7 The supportive data for Table 14.1.7 will be presented in Listing 16.6.1 entitled *Neurologic Status.* This listing will be sorted by time point / visit, clinical site and patient number.

8.7. Medical Status Recorded at Screening

All enrolled patients will be included in Table 14.1.8 entitled *Summary of Solicited Medical Status and Life Style Preferences Recorded at Screening*. Results will be presented for each of the following 3 groups

- Patients randomized to the Solitaire device (Treatment Group 1),
- Patients randomized to the pRESET Group (Treatment Group 2), and
- All randomized patients

The solicited events are as follows:

- Previous Stroke / TIA (yes or no)
- Previous MI / CAD (yes or no)
- Hypertension (yes or no)
- Atrial Fibrillation (yes or no)
- Alcohol and/or Illicit Drug abuse (yes or no)
- Diabetes Mellitus (yes or no)
- Dyslipidaemia (yes or no)
- Renal Disease (yes or no)
- Obesity (yes or no)
- Sleep Apnea (yes or no)
- Smoker (yes or no)
- Other Pre-existing Medical Condition (yes or no)

The responses will be summarized using counts and percentages and compared between the randomized treatment groups using a Fisher's Exact test. **Patients with missing data that cannot**

be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics.

The supportive data for Table 14.1.8 will be presented in Listing 16.4.4 entitled *Summary of Solicited Medical Status and Life Style Preferences Recorded at Screening* The listings will include the event (yes or no), start date, finish date, and if the event was treated. This listing will be sorted by clinical site and patient number.

8.8. Imaging Findings, ASPECT Scores, and Barthel Index Recorded at Screening

All enrolled patients will be included in Table 14.1.9 entitled *Summary of Imaging Findings, ASPECT Scores, and Barthel Index Recorded at Screening*. Results will be presented for each of the following 3 groups

- Patients randomized to the Solitaire device (Treatment Group 1),
- Patients randomized to the pRESET Group (Treatment Group 2), and
- All randomized patients

The solicited findings and information are as follows:

- Imaging modality (CT, MRI, other)
- MR or CT Angiography
- Hemorrhage (yes or no)
- Mass effect or Intra-cranial tumor (yes or no)
- Cerebral Vasculitis (yes or no)
- Evidence of carotid dissection or complete cervical carotid occlusion (yes or no)
- Occlusions in multiple vascular territories (yes or no)
- ASPECTS Score
- Core Infarct Size (cc)
- Barthel Index

The responses will be summarized using counts and percentages and compared between the randomized treatment groups using a Fisher's Exact test. **Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics.**

The ASPECT scores and Barthel index will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, range (*i.e.*, minimum and maximum values) and compared between the randomized treatment groups using a one-factor (randomized treatment assignment) analysis of variance test. The supportive data for Table 14.1.9 will be presented in 16.4.5 - Part 1 entitled Imaging Findings and ASPECT Scores at Screening - Part 1 of 2 and 16.4.5 - Part 2 entitled Imaging Findings and ASPECT Scores at Screening - Part 2 of 2. This listing will be sorted by clinical site and patient number.

9. STUDY PROCEDURE AND DEVICE ACCOUNTABILITY

This section will discuss the tabulation and analysis of the study procedure, device accountability parameters, and efficacy. Detailed descriptions of the statistical models that will be used to analyze the study endpoints will be described below.

9.1. Study Procedure

The tabulations and analyses relative to the study procedure are presented in the following 3 tables (14.2.1, 14.2.2, and 14.2.2.1).

All patients in the ITT population will be included in Table 14.2.1 entitled *Summary of the Target Vessel and Ischemic Occlusion*. The source of the data will be the Core Lab file. Results will be presented for each of the following 3 groups

- Patients randomized to the Solitaire device (Treatment Group 1),
- Patients randomized to the pRESET Group (Treatment Group 2), and
- All randomized patients.

Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics. The count and frequency for the type of anesthesia (elective general, emergent general, local, and light sedation) and vascular closure method will be summarized and compared between the randomized device groups using a two-tailed Fisher's exact test. The time segments from time from stroke onset and groin puncture to closure will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, range (*i.e.*, minimum and maximum values) and compared between the randomized treatment assignments using a mixed model.

The following target vessel information from the EDC system will be summarized by randomized treatment assignment:

Was a proximal stenosis present? (yes, no)
If Yes, Location:
Left ICA (yes, no)
Right ICA (yes, no)
Left VA (yes, no)
Right VA (yes, no)
Other (yes, no)

Target occlusion location:
Left Hemisphere (yes, no)
Right Hemisphere (yes, no)
Posterior (yes, no)
If Right / Left Hemisphere, specify locations:
Carotid T (incl. ICA, M1 and A1) (yes, no)
Cervical ICA (yes, no)
MCA – M1 – Proximal 1/3 (yes, no)
MCA – M1 – Middle 1/3 (yes, no)

MCA – M1 – Distal 1/3 (yes, no)
MCA – M2 – Anterior Branch (yes, no)
MCA – M2 – Middle Branch (yes, no)
MCA – M2 – Posterior Branch (yes, no)
Other (yes, no)

If Posterior location:
BA – Proximal 1/3 (yes, no)
BA – Middle 1/3 (yes, no)
BA – Distal 1/3, bifurcation (yes, no)
Other (yes, no)

The number and percentage of patients by target vessel location will also be presented. The tabulation of patients across the different vessels is independent; multiple patients can have multiple occluded vessels. Results will be presented based on the number of responses in each category using counts and percentages. The proportion of patients with and without a specific occluded vessel will be compared between the randomized device groups using a two-tailed Fisher's exact test.

A summary of the devices used during the procedure will be presented. The following list of devices is presented below. Results will be summarized using counts and percentages.

- Sheath (8 F, 6 F, 5 F, Other F)
- Micro guidewire (name)
- Guide Catheter (8 F, 6 F, Other F)
- Balloon Guide Catheter (yes, no)
- Microcatheter (name)
- Distal Access Catheter (yes, no)

A summary of the intervention will be presented. Results will be summarized using counts and percentages.

- eTICI Pre-first pass: (0, 1, 2a, 2b50, 2b67, 2c, 3)
- Was clot fully retrieved: (yes, no)
- eTICI Post-first pass: (0, 1, 2a, 2b50, 2b67, 2c, 3)

- Second Pass required: (yes, no)
- eTICI Pre-Second pass: (0, 1, 2a, 2b50, 2b67, 2c, 3)
- Was clot fully retrieved: (yes, no)
- eTICI Post-second pass: (0, 1, 2a, 2b50, 2b67, 2c, 3)

- Third Pass required: (yes, no)
- eTICI Pre-third pass: (0, 1, 2a, 2b50, 2b67, 2c, 3)
- Was clot fully retrieved: (yes, no)
- eTICI Post-third pass: (0, 1, 2a, 2b50, 2b67, 2c, 3)

- Was any rescue therapy used? (yes, no)
- What rescue therapy was required:
    - Mechanical Thrombectomy device
    - Aspiration Catheter
    - Intracranial stenting
    - Other

- Angiographic evidence of new territory embolization (yes, no)

Blood pressure post procedure will be summarized using descriptive statistics.

The supportive data for Table 14.2.1 will be presented in Listing 16.4.6 entitled *Occlusion Information*. This listing will be sorted by clinical site and patient number.

All patients in the ITT population randomized to undergo the study procedure will be included in Table 14.2.2 entitled *Summary of the Study Device Procedure.* Results will be presented for each of the following 3 groups

- Patients randomized to the Solitaire device (Treatment Group 1),
- Patients randomized to the pRESET Group (Treatment Group 2), and
- All randomized patients.

The maximum intra-patient number of passes, clot retrieval, and procedure time (minutes) will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, and range (*i.e.*, minimum and maximum values). The procedure time will be compared between the randomized treatment assignments using a one-factor (randomized treatment assignment) analysis of variance test. The number of passes are counts and will be compared between the randomized treatment assignments using a Wilcoxon 2-sample test**. Patients with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics.**

The supportive data for Table 14.2.2 will be presented in Listing 16.4.7 entitled *Study Device Procedure*. This listing will be sorted by clinical site and patient number.

Table 14.2.2.1 entitled *Target Vessel Location* will contain the location of the target vessel based on the Stroke Drop dataset.

9.2. Study Device Accountability

A summary of study device accountability for the ITT population will be presented in Listing 16.4.8 entitled *Study Device Accountability*. This listing will be sorted by clinical site and patient number.

10. EFFECTIVENESS EVALUATIONS AND FOLLOW-UP VISIT ASSESSMENTS

10.1. Analysis of the Primary Effectiveness Endpoint

The results will be presented for all 3 analysis populations: the ITT population is the primary population for determining the results from this study. The per-protocol population and the as-treated populations will be used to frame the sensitivity analyses.

The primary effectiveness endpoint of this study maps to the primary effectiveness objective and addresses the following research question:

After 90 days following the procedure, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in global disability (mRS ≤ 2) above the a priori threshold of -12.5%?

The hypothesis is that the proportion of good outcomes (mRS ≤ 2) at 90 days after treatment with the pRESET thrombectomy device in patients with cerebral infarction is non-inferior to the rate of good outcome at 90 days after treatment with the Solitaire device. The largest clinically acceptable effect to be able to declare non-inferiority is -12.5% (non-inferiority margin). The null and alternative hypotheses can be defined mathematically as follows:

- H_o: Treatment with pRESET is inferior to treatment with Solitaire for good outcomes defined as an mRS ≤ 2 at 90 days based on a non-inferiority margin of -12.5% (good outcome with pRESET < [good outcome with Solitaire – 12.5%]).
- H_a: Treatment with pRESET is non-inferior to treatment with Solitaire for good outcome defined as an mRS ≤ 2 at 90 days based on a non-inferiority margin of -12.5% (good outcome with pRESET ≥ [good outcome with Solitaire – 12.5%])

The SAS code to generate these summary statistics and addressing missing mRS data at 90 days post-procedure is presented below. The imputation will be conducted by treatment assignment and the resulting proportions from the individual treatment groups will be used to calculated the confidence interval of the difference. The factors listed below will be used in the model.

- Age: ≥65 and <65 [AGE_CAT]
- Site of occlusion: ICA, MCA and BA [RANDOM_LOC]
- Baseline/Enrollment NIHSS score: <17 and ≥17 [RANDOM_NIHSS]
- Prior IV t-PA usage: Yes and No [RANDOM_IVTPA]
- Time to symptom onset: ≥4 hours and <4 hours [RANDOM_ONSET]
- pRESET (1) and Solitare (2) [TRTN]

***Multiple imputation for patients without an mRS at 90 days (Run separately for each randomized treatment group);**

SAS Code for the active treatment is presented below.

```
proc mi data=ACTIVE out=ACTIVE_mi SEED=207890 NIMPUTE=10;
```

```
class SUBJID MRS_BIN AGE_CAT RANDOM_LOC RANDOM_NIHSS RANDOM_IVTPA
RANDOM_ONSET;

fcs discrim (MRS_BIN = SUBJID AGE_CAT RANDOM_LOC RANDOM_NIHSS
RANDOM_IVTPA RANDOM_ONSET /classeffects=include);

var SUBJID MRS_BIN AGE_CAT RANDOM_LOC RANDOM_NIHSS RANDOM_IVTPA
RANDOM_ONSET;

run;


proc freq data=ACTIVE_mi;
tables MRS_BIN / cl binomial;
by _imputation_;
ods output binomial=prop_ACTIVE;
RUN;
data prop2_ACTIVE;
merge
prop_ACTIVE(where=(Label1="Proportion")
keep=_imputation_ nValue1 Label1
rename=(nValue1=prop))
prop_ACTIVE(where=(Label1="ASE")
keep=_imputation_ nValue1 Label1
rename=(nValue1=prop_se));
by _imputation_;
run;
DATA prop2_ACTIVE;
SET prop2_ACTIVE;
TRTN = 1;
RUN;
* Combine proportion estimates by mianalyze;
proc sort data=prop2_ACTIVE; by _imputation_; RUN;
proc mianalyze data=prop2_ACTIVE ;
modeleffects prop;
stderr prop_se;
ods output parameterestimates=mi_effout_ACTIVE;
run;
DATA ACTIVE_EVENT;
SET mi_effout_ACTIVE;
COUNT = ROUND(&N1 * ESTIMATE);
EVENT = 1;
TRTN = 1;
KEEP TRTN EVENT COUNT;
RUN;
DATA ACTIVE_NO_EVENT;
SET mi_effout_ACTIVE;
ESTIMATE_COMPLEMENT = 1 - ESTIMATE;
RUN;
DATA ACTIVE_NO_EVENT;
```

```
SET ACTIVE_NO_EVENT;
COUNT = ROUND(&N1 * ESTIMATE_COMPLEMENT);
EVENT = 2;
TRTN = 1;
KEEP TRTN EVENT COUNT;
RUN;
DATA ACTIVE_RESULT;
SET
ACTIVE_EVENT
ACTIVE_NO_EVENT;
RUN;
```

SAS Code for the control treatment is presented below.

```
proc mi data=CONTROL out=CONTROL_mi SEED=207890 NIMPUTE=10;
class SUBJID MRS_BIN AGE_CAT RANDOM_LOC RANDOM_NIHSS RANDOM_IVTPA
RANDOM_ONSET;
fcs discrim (MRS_BIN = SUBJID AGE_CAT RANDOM_LOC RANDOM_NIHSS
RANDOM_IVTPA RANDOM_ONSET /classeffects=include);
var SUBJID MRS_BIN AGE_CAT RANDOM_LOC RANDOM_NIHSS RANDOM_IVTPA
RANDOM_ONSET;
run;
proc freq data=CONTROL_mi;
tables MRS_BIN / cl binomial;
by _imputation_;
ods output binomial=prop_CONTROL;
RUN;
data prop2_CONTROL;
merge
prop_CONTROL(where=(Label1="Proportion")
keep=_imputation_ nValue1 Label1
rename=(nValue1=prop))
prop_CONTROL(where=(Label1="ASE")
keep=_imputation_ nValue1 Label1
rename=(nValue1=prop_se));
by _imputation_;
run;
DATA prop2_CONTROL;
SET prop2_CONTROL;
TRTN = 2;
RUN;
* Combine proportion estimates by mianalyze;
proc sort data=prop2_CONTROL; by _imputation_; RUN;
proc mianalyze data=prop2_CONTROL ;
modeleffects prop;
stderr prop_se;
ods output parameterestimates=mi_effout_CONTROL;
```

```
run;
DATA CONTROL_EVENT;
SET mi_effout_CONTROL;
COUNT = ROUND(&N1 * ESTIMATE);
EVENT = 1;
TRTN = 2;
KEEP TRTN EVENT COUNT;
RUN;
DATA CONTROL_NO_EVENT;
SET mi_effout_CONTROL;
ESTIMATE_COMPLEMENT = 1 - ESTIMATE;
RUN;
DATA CONTROL_NO_EVENT;
SET CONTROL_NO_EVENT;
COUNT = ROUND(&N1 * ESTIMATE_COMPLEMENT);
EVENT = 2;
TRTN = 2;
KEEP TRTN EVENT COUNT;
RUN;
DATA CONTROL_RESULT;
SET
CONTROL_EVENT
CONTROL_NO_EVENT;
RUN;
PROC PRINT DATA = CONTROL_RESULT;
RUN;

DATA ACTIVE_CONTROL;
SET
ACTIVE_RESULT
CONTROL_RESULT;
RUN;
```

Dataset mi_out will have the imputed results for each treatment group. This file will be used for calculating the proportions. The SAS code presented below will be used to calculate the confidence interval of the difference:

```
ODS TRACE ON;
ODS OUTPUT RISKDIFFCOL1 = RD_001;
ODS OUTPUT CROSSTABFREQS = FREQ_001;
proc freq data = ACTIVE_CONTROL;
table TRTN * EVENT / exact relrisk riskdiff alpha=0.10;
weight count;
run;

proc freq data = proportions_001;
table TREAT_N * PROPORTION_MRS_0_2 / exact relrisk riskdiff alpha=0.10;
```

```
weight count;
run;
```

The primary endpoint results will be presented in Table 14.4.1 entitled *Modified Rankin Scale (mRS) Scores 0-2 Results by Randomized Treatment Assignment and Time*. Results will be presented for the following 2 groups:

- Patients randomized to the Solitaire device (Treatment Group 1), and
- Patients randomized to the pRESET Group (Treatment Group 2)

If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in global disability is numerically greater than -12%, pRESET will be considered non-inferior to Solitaire.

Additionally, as a sensitivity analysis of the primary endpoint, a logistic model will be performed. This model will incorporate the stratification variables specified in the randomization as covariates and with randomization group assignment. The example SAS code to generate this analysis is presented below, beginning with the imputation and ending with the MIANALYZE results.

```
proc mi data=ADEFF seed=1305417 out=ADEFF_001_OUT;
  class MRS_BIN TRTN RANDOM_LOC RANDOM_AGE RANDOM_NIHSS
RANDOM_IVTPA RANDOM_ONSET;
  monotone logistic( MRS_BIN = TRTN RANDOM_LOC RANDOM_AGE RANDOM_NIHSS
RANDOM_IVTPA RANDOM_ONSET/ DETAILS LIKELIHOOD=AUGMENT);
  var TRTN RANDOM_LOC RANDOM_AGE RANDOM_NIHSS RANDOM_IVTPA
RANDOM_ONSET MRS_BIN;
run;
PROC SORT DATA = ADEFF_001_OUT;
BY _IMPUTATION_;
RUN;
ODS TRACE ON;
ODS OUTPUT LSMEANS = LSMEANS_001;
ODS OUTPUT PARAMETERESTIMATES = PARAM_001;
ODS OUTPUT DIFFS = DIFFS_001;
PROC GLIMMIX data=ADEFF_001_OUT METHOD=RSPL;
BY _IMPUTATION_;
  class MRS_BIN TRTN RANDOM_LOC RANDOM_AGE RANDOM_NIHSS
RANDOM_IVTPA RANDOM_ONSET;
  model MRS_BIN = TRTN RANDOM_LOC RANDOM_AGE RANDOM_NIHSS
RANDOM_IVTPA RANDOM_ONSET/ ddfm=residual DIST=binary link=log S cl alpha = 0.1;
  CONTRAST "PRESET VS. SOLITAIRE" TRTN -1 1 / EST;
  ESTIMATE  "PRESET VS. SOLITAIRE" TRTN -1 1 / CL;
  LSMEANS TRTN / PDIFF CL;
run;
ODS OUTPUT CLOSE;
PROC PRINT DATA = LSMEANS;
PROC PRINT DATA = PARAM_001;
```

```
PROC PRINT DATA = DIFFS_001;
DATA DIFFS_001;
SET DIFFS_001;
IF EFFECT = "TRTN" AND TRTN = 1 THEN OUTPUT;
KEEP _IMPUTATION_ ESTIMATE STDERR  LOWER UPPER;
RUN;

proc sort data=DIFFS_001; by _IMPUTATION_; RUN;

proc mianalyze data=DIFFS_001 ALPHA = 0.1;
modeleffects ESTIMATE;
stderr;
  ods output parameterestimates=mi_effout;
run;
PROC PRINT DATA = MI_EFFOUT;
RUN;
```

The results will be presented using the imputed data in Table 14.4.1.1 for the ITT population entitled *Summary of the Logistic Modeling of the Modified Rankin Scale (mRS) Scores 0-2 Results (imputed) by Randomized Treatment Assignment and Time*.

The results will be presented using the observed / non-imputed data in Table 14.4.1.2 for the ITT population entitled *Summary of the Logistic Modeling of the Modified Rankin Scale (mRS) Scores 0-2 Results (observed) by Randomized Treatment Assignment and Time* and Table 14.1.2a entitled *Summary of the Risk Difference of the Modified Rankin Scale (mRS) Scores 0-2 Results (observed) by Randomized.*

Separate sub-group analysis will be prepared to examine factors that may have influenced the 90-day mRS scores. The same procedure will be used for each factor. Results are presented in the following 3 tables:

14.4.1.3a Modified Rankin Scale (mRS) Scores 0-2 Results by Randomized Group and Age (>80 and ≤80)
14.4.1.3b Modified Rankin Scale (mRS) Scores 0-2 Results by Randomized Group and Age (>70 and ≤70)
14.4.1.3c Modified Rankin Scale (mRS) Scores 0-2 Results by Randomized Group and Age (≥65 and <65)

Patients with missing observations for this endpoint will be excluded from the analysis. The distribution of patients by mRS score will be presented by randomized treatment assignment using counts and percentages. Results from the Breslow-Day test of homogeneity will be presented to evaluate the interaction between treatment and age; a probability value ≥0.05 will indicate that the treatment effect pRESET vs. Solitaire) did not differ significantly.

The PROC FREQ SAS code will be used to create a multiway table stratified separately for each parameter, where Treatment forms the rows and Response forms the columns. The CMH option

produces the Cochran-Mantel-Haenszel statistics. For this stratified table, estimates of the common relative risk and the Breslow-Day test for homogeneity of the odds ratios will also be presented.

```
ODS OUTPUT BreslowDayTest = BD_001;
PROC FREQ DATA = ADEFF;
BY OB_TIME_N;
TABLE RANDOM_AGE * COHORT_N * MRS_02 / CMH;
RUN;
ODS OUTPUT CLOSE;
PROC PRINT DATA = BD_001;
RUN;
DATA BD_001;
SET BD_001;
IF NAME1 = "P_BDCHI" THEN OUTPUT;
KEEP OB_TIME_N CVALUE1;
RUN;
DATA BD_001;
FORMAT LABEL $100.;
SET BD_001;
ORD = 1;
ORDER = 4;
VAL1 = COMPRESS(CVALUE1);
LABEL = "Breslow-Day Test";
KEEP OB_TIME_N ORD ORDER VAL1 LABEL;
RUN;
```

Table series 14.4.1.3 will be repeated for Site of occlusion: ICA, MCA and BA (Table 14.4.1.4), Baseline/Enrollment NIHSS score: <17 and ≥17 (Table 14.4.1.5), Prior IV t-PA usage: Yes and No (Table 14.4.1.6), and Time to symptom onset: ≥4 hours and <4 hours (Table 14.4.1.7).

The supportive data for Tables 14.4.1 through 14.4.1.7 will be presented in Listing 16.6.1 entitled *Neurologic Status*. This listing will be sorted by clinical site and patient number.

Table 14.4.1.8 entitled *Modified Rankin Scale (mRS) Scores 0-2 Results by Randomized Group Based on the Last Recorded mRS Score* (Sensitivity Analysis) and Table 14.4.1.9 entitled *Tipping Point Analysis for the Modified Rankin Scale (mRS) Scores 0-2 Results by Randomized Group* will also be generated.

10.2. Secondary Endpoint 2: Proportion of Patients with eTICI 2c or Greater Flow in the Target Vessel Post-Procedure Following the First Pass

The research question for the second secondary endpoint is presented below:

*Following the **first pass** of the assigned study device, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with*

eTICI 2c or greater flow in the target vessel post-procedure above the a priori threshold of -12.1%?

The hypothesis is that the proportion of patients with eTICI 2c or greater flow in the target vessel post-procedure is non-inferior to the patients treatment with the Solitaire device. The largest clinically acceptable effect to be able to declare non-inferiority is -12.1% (non-inferiority margin). The null and alternative hypotheses can be defined mathematically as follows:

- H_o: Treatment with pRESET is inferior to treatment with Solitaire for eTICI 2c or greater flow in the target vessel post-procedure based on a non-inferiority margin of -12.1%.
- H_a: Treatment with pRESET is non-inferior to treatment with Solitaire for eTICI 2c or greater flow in the target vessel post-procedure based on a non-inferiority margin of -12.1%.

If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2c or greater flow in the target vessel post-procedure is numerically greater than -12.1%, pRESET will be considered non-inferior to Solitaire.

The SAS code to generate these summary statistics and addressing missing post-procedure is presented in Section 10.1 for the primary endpoint. With the exception of the different dependent variable, the same SAS code and procedure is applicable.

The results will be presented in the following tables that follow the format of the 14.4.2 tables:

14.4.3 (Part 2) TICI Results [eTICI 2c or greater / First Pass] (imputed) by Randomized Treatment Assignment
14.4.3.1 Summary of the Logistic Modeling of the TICI Results [eTICI 2c / First Pass] (imputed) by Randomized Treatment Assignment
14.4.3.2 Summary of the Logistic Modeling of the TICI Results [eTICI 2c / First Pass] (observed) by Randomized Treatment Assignment
14.4.3.3a TICI Results [eTICI 2c / First Pass] (observed) Results by Randomized Group and Age (>80 and ≤80)
14.4.3.3b TICI Results [eTICI 2c / First Pass] (observed) Results by Randomized Group and Age (>70 and ≤70)
14.4.3.3c TICI Results [eTICI 2c / First Pass] (observed) Results by Randomized Group and Age (>=65 and <65)
14.4.3.4 TICI Results [eTICI 2c / First Pass] (observed) Results by Randomized Group and Occlusion Site Location
14.4.3.5 TICI Results [eTICI 2c / First Pass] (observed) Results by Randomized Group and Baseline/Enrollment NIHSS score (<17 and >=17)
14.4.3.6 TICI Results [eTICI 2c / First Pass] (observed) Results by Randomized Group and Prior IV t-PA usage: Yes and No
14.4.3.7 TICI Results [eTICI 2c / First Pass] (observed) Results by Randomized Group and Time to Symptom Onset >=4 hours and <4 hours

The supportive data for Tables 14.4.3 through 14.4.3.7 will be presented in the following listings:

16.7.1 - Part 1 of 2 TICI Results - Part 1 of 2
16.7.1 - Part 2 of 2 TICI Results - Part 2 of 2

These listing will be sorted by clinical site and patient number.

10.3. Secondary Endpoint 1: Proportion of Patients with eTICI 2b50 or Greater Flow in the Target Vessel Post-Procedure Based on the Best eTICI Result Within ≤3 Passes

The results will be based on the last pass which may be the first, second, or third pass.
The research question for the first secondary endpoint is presented below:

*Following a **maximum of 3 passes** of the assigned study device,* based on the best eTICI result within ≤3 passes, *is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50 or greater flow in the target vessel post-procedure above the a priori threshold of -12.1%?*

The hypothesis is that the proportion of patients with eTICI 2b50 or greater flow in the target vessel post-procedure is non-inferior to the patients treatment with the Solitaire device. The largest clinically acceptable effect to be able to declare non-inferiority is -12.1% (non-inferiority margin). The null and alternative hypotheses can be defined mathematically as follows:

- H_o: Treatment with pRESET is inferior to treatment with Solitaire for eTICI 2b50 or greater flow in the target vessel post-procedure based on a non-inferiority margin of -12.1%.
- H_a: Treatment with pRESET is non-inferior to treatment with Solitaire for eTICI 2b50 or greater flow in the target vessel post-procedure based on a non-inferiority margin of -12.1%.

If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50 or greater flow in the target vessel post-procedure is numerically greater than -12.1%, pRESET will be considered non-inferior to Solitaire.

The SAS code to generate these summary statistics and addressing missing data post-procedure is presented in Section 10.1 for the primary endpoint. With the exception of the different dependent variable, the same SAS code and procedure is applicable.

The results will be presented in the following tables:

14.4.2 (Part 1) TICI Results [eTICI 2b50 / Final Pass] (imputed) Following a Maximum of 3 Passes by Randomized Treatment Assignment
14.4.2.1 Summary of the Logistic Modeling of the TICI Results [eTICI 2b50 / Final Pass] (imputed) Following a Maximum of 3 Passes by Randomized Treatment Assignment
14.4.2.2 Summary of the Logistic Modeling of the TICI Results [eTICI 2b50 / Final Pass] (observed) Following a Maximum of 3 Passes by Randomized Treatment Assignment

14.4.2.2a Summary of the Risk Difference of the TICI Results [eTICI 2b50 / Final Pass] (observed) Following a Maximum of 3 Passes (observed) by Randomized Treatment Assignment (ITT Population)
14.4.2.3a TICI Results [eTICI 2b50 / Final Pass] (observed) Results by Randomized Group and Age (>80 and ≤80)
14.4.2.3b TICI Results [eTICI 2b50 / Final Pass] (observed) Results by Randomized Group and Age (>70 and ≤70)
14.4.2.3c TICI Results [eTICI 2b50 / Final Pass] (observed) Results by Randomized Group and Age (>=65 and <65)
14.4.2.4 TICI Results [eTICI 2b50 / Final Pass] (observed) Results by Randomized Group and Occlusion Site Location
14.4.2.5 TICI Results [eTICI 2b50 / Final Pass] (observed) Results by Randomized Group and Baseline/Enrollment NIHSS score (<17 and >=17)
14.4.2.6 TICI Results [eTICI 2b50 / Final Pass] (observed) Results by Randomized Group and Prior IV t-PA usage: Yes and No
14.4.2.7 TICI Results [eTICI 2b50 / Final Pass] (observed) Results by Randomized Group and Time to Symptom Onset >=4 hours and <4 hours

Additionally, as a sensitivity analysis of this endpoint, an analysis using a logistic model will be performed. This model will incorporate the stratification variables specified in the randomization as covariates and with randomization group assignment. With the exception of the different dependent variable, the same SAS code and procedure used for the primary endpoint. The results will be presented using the observed / non-imputed data in Table 14.4.2.2 for the ITT population entitled *Summary of the Logistic Modeling of the TICI Results (observed) Following a Maximum of 3 Passes by Randomized Treatment Assignment and Time*.

The supportive data for Tables 14.4.2 through 14.4.2.7 will be presented in the following listings:

16.7.1 - Part 1 of 2 TICI Results - Part 1 of 2
16.7.1 - Part 2 of 2 TICI Results - Part 2 of 2

These listing will be sorted by clinical site and patient number.

10.4. Secondary Endpoint 3: Mortality at 90 Days Post-Procedure

The research question for the third secondary endpoint is presented below:

Ninety days following the index stroke, is the upper bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in mortality below the a priori threshold of 10%?

The hypothesis is that the proportion of patients who die is not significantly difference between the randomized treatment groups. The null and alternative hypotheses can be defined mathematically as follows:

- H_o: Treatment with pRESET is inferior to treatment with Solitaire for mortality at 90 days post-procedure based on a non-inferiority margin of 10%.
- H_a: Treatment with pRESET is non-inferior to treatment with Solitaire for mortality at 90 days post-procedure based on a non-inferiority margin of 10%.

If the upper bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in mortality is numerically less than 10%, pRESET will be considered non-inferior to Solitaire.

The results will be presented in the following tables that follow the format of the 14.4.4 tables:

14.4.4.1	Summary of the Logistic Modeling of the Mortality Results (imputed) Randomized Treatment Assignment
14.4.4.2	Summary of the Logistic Modeling of the Mortality Results (observed) Randomized Treatment Assignment
14.4.4.3a	Mortality at 90 Days Post-Procedure by Randomized Group and Age (>80 and ≤80)
14.4.4.3b	Mortality at 90 Days Post-Procedure by Randomized Group and Age (>70 and ≤70)
14.4.4.3c	Mortality at 90 Days Post-Procedure by Randomized Group and Age (≥65 and <65)
14.4.4.4	Mortality (observed) Results by Randomized Group and Occlusion Site Location
14.4.4.5	Mortality at 90 Days Post-Procedure by Randomized Group and Baseline/Enrollment NIHSS score: <17 and ≥17
14.4.4.6	Mortality at 90 Days Post-Procedure by Randomized Group and Prior IV t-PA usage: Yes and No
14.4.4.7	Mortality at 90 Days Post-Procedure by Randomized Group and Time to symptom onset: ≥4 hours and <4 hours

The supportive data for Tables 14.4.4 through 14.4.4.7 will be presented in Listing 16.8.1 entitled *Mortality Results*. This listing will be sorted by clinical site and patient number.

10.5. Secondary Endpoint 4: mRS Shift at 90 Days Post-Procedure

The research question for the fourth secondary endpoint is presented below:

After 90 days following the stroke, using a proportional odds model (ordinal logistic regression) with an assumed common odds ratio of improvement on the mRS, is the confidence interval of the upper bound of the odds ratio less than 0.875, suggesting the shift towards better outcomes across the entire spectrum of disability is more than 12.5% better with Solitaire compared to pRESET?

The factors listed below will be used in the imputation.

- Age: ≥65 and <65 [RANDOM_AGE]
- Site of occlusion: ICA, MCA and BA [RANDOM_LOC]
- Baseline/Enrollment NIHSS score: <17 and ≥17 [RANDOM_NIHSS]
- Prior IV t-PA usage: Yes and No [RANDOM_IVTPA]
- Time to symptom onset: ≥4 hours and <4 hours [RANDOM_ONSET]
- pRESET (1) and Solitare (2) [TRTN]

The adjusted odds ratio with the 95% confidence intervals will be presented.

Results will be presented in Table 14.4.5 entitled *Modified Rankin (mRS) Shift Analysis at 90 Days*. The supportive data for Table 14.4.5 will be presented in Listing 16.6.1 entitled *Neurologic Status*. This listing will be sorted by clinical site, patient number and time point of collection.

10.6. Exploratory Endpoints

10.6.1. Exploratory Endpoint 2: Proportion of Patients with eTICI 2c or Greater Flow in the Target Vessel Post-Procedure Based on the Best eTICI Result Within ≤3 Passes

The research question for this endpoint is presented below:

Following the last pass (≤3 passes) of the assigned study device, and based on the best eTICI result within ≤3 passes, *is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2c or greater above the a priori threshold of --12.1%?*

The hypothesis is that the proportion of patients with eTICI 2c or greater flow is non-inferior to the patients treatment with the Solitaire device. The largest clinically acceptable effect to be able to declare non-inferiority is -12.1% (non-inferiority margin). The null and alternative hypotheses can be defined mathematically as follows:

- H_o: Treatment with pRESET is inferior to treatment with Solitaire for eTICI 2c or greater flow based on a non-inferiority margin of -12.1%.
- H_a: Treatment with pRESET is non-inferior to treatment with Solitaire for eTICI 2c or greater flow based on a non-inferiority margin of -12.1%.

If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2c or greater flow is numerically greater than -12.1%, pRESET will be considered non-inferior to Solitaire.

The SAS code to generate these summary statistics and addressing missing is presented in Section 10.1 for the primary endpoint. With the exception of the different dependent variable, the same SAS code and procedure is applicable.

The results will be presented in Table 14.4.7.1 entitled *TICI 2c or Greater Flow Following the Final Pass by Randomized Treatment*. The supportive data for Tables 14.4.7.1 will be presented in Listing 16.7.1 entitled *TICI Results*. This listing will be sorted by clinical site and patient number.

10.6.2. Exploratory Endpoint 3: Proportion of Patients with eTICI 2b50 or Greater and eTICI 2c or Greater in the Target Vessel Post-Procedure Following the Final Pass

The research question for this endpoint is presented below:

*Following the **final pass** (≤3 passes) of the assigned study device, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50 or greater flow and eTICI 2c or greater flow above the a priori threshold of -12.1%?*

The hypothesis is that the proportion of patients with eTICI 2b50 *or greater flow* and eTICI 2c *or greater flow* is non-inferior to the patients treatment with the Solitaire device. The largest clinically acceptable effect to be able to declare non-inferiority is -12.1% (non-inferiority margin). The null and alternative hypotheses can be defined mathematically as follows:

- H_o: Treatment with pRESET is inferior to treatment with Solitaire for eTICI 2b50 or greater flow and eTICI 2c or greater flowbased on a non-inferiority margin of -12.1%.
- H_a: Treatment with pRESET is non-inferior to treatment with Solitaire for eTICI 2b50 or greater flow and eTICI 2c or greater flow based on a non-inferiority margin of -12.1%.

If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50 *or greater flow* or eTICI 2c *greater flow* is numerically greater than -12.1%, pRESET will be considered non-inferior to Solitaire.

The results will be presented in Table 14.4.7.2 entitled *TICI 2b50 or Greater Flow Following the Final Pass by Randomized Treatment*. The supportive data for Tables 14.4.7.1 will be presented in Listing 16.7.1 entitled *TICI Results*. This listing will be sorted by clinical site and patient number.

10.6.3. Exploratory Endpoint 4: Proportion of Patients with eTICI 2b50, 2b67, 2c or 3 Flow in the Target Vessel Post-Procedure Following the First Pass

The research question for this endpoint is presented below:

*Following the **first pass** of the assigned study device, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50, 2b67, 2c or 3 flow in the target vessel post-procedure above the a priori threshold of -12.1%?*

The hypothesis is that the proportion of patients with eTICI 2b50, 2b67, 2c or 3 flow in the target vessel post-procedure is non-inferior to the patients treatment with the Solitaire device. The largest clinically acceptable effect to be able to declare non-inferiority is -12.1% (non-inferiority margin). The null and alternative hypotheses can be defined mathematically as follows:

- H_o: Treatment with pRESET is inferior to treatment with Solitaire for eTICI 2b50, 2b67, 2c or 3 flow in the target vessel post-procedure based on a non-inferiority margin of -12.1%.
- H_a: Treatment with pRESET is non-inferior to treatment with Solitaire eTICI 2b50, 2b67, 2c or 3 flow in the target vessel post-procedure based on a non-inferiority margin of -12.1%.

If the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with eTICI 2b50, 2b67, 2c or 3 flow in the target vessel post-procedure is numerically greater than -12.1%, pRESET will be considered non-inferior to Solitaire.

The results will be presented in Table 14.4.7.3 entitled *TICI Results (eTICI 2b50, 2b67, 2c or 3) Following the Final Pass by Randomized Treatment Assignment*. The supportive data for Table

14.4.7.3 will be presented in Listing 16.7.1 entitled *TICI Results*. This listing will be sorted by clinical site and patient number.

10.6.4. Exploratory Endpoint 1: Proportion of Patients with mRS ≤ 1 at 90 days

The research question for this endpoint is presented below:

After 90 days following the stroke, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in global disability (mRS ≤ 1) above the a priori threshold of -12.5%?

The hypothesis is that the proportion of good outcomes (mRS ≤ 1) at 90 days after the stroke with the pRESET thrombectomy device in patients with cerebral infarction is non-inferior to the rate of good outcome at 90 days after the stroke with the Solitaire device. The largest clinically acceptable effect to be able to declare non-inferiority is -12.5% (non-inferiority margin). The null and alternative hypotheses can be defined mathematically as follows:

- H_o: Treatment with pRESET is inferior to treatment with Solitaire for an mRS ≤ 1 at 90 days based on a non-inferiority margin of -12.5% (mRS ≤ 1 at 90 days with pRESET < [mRS ≤ 1 at 90 days with Solitaire – 12.5%]).
- H_a: Treatment with pRESET is non-inferior to treatment with Solitaire for an mRS ≤ 1 at 90 days based on a non-inferiority margin of -12.5% (mRS ≤ 1 at 90 days with pRESET ≥ [mRS ≤ 1 at 90 days with Solitaire – 12.5%])

The same statistical model used for table 14.4.1 will be used for this analysis.

The results will be presented in Table 14.4.6 entitled *Modified Rankin Scale (mRS) Scores 0-1 Results by Randomized Treatment Assignment at 90-Days Post-Treatment (ITT Population with multiple imputation for patients.* The supportive data for Table 14.4.6 will be presented in Listing 16.6.1 entitled *Neurologic Status*. This listing will be sorted by clinical site and patient number.

10.6.5. Exploratory Endpoint 5: Proportion of Patients with an Early Response at Day 7/Discharge defined as a NIHSS reduction of ≥10 points from baseline or an NIHSS score 0 or 1

The research question for this endpoint is presented below:

Does the 2-sided 95% binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients classified as early responders at Day 7/Discharge (whichever is earlier), contain zero?

An early responder is a patient with a NIHSS drop of ≥10 points from baseline or an NIHSS score 0 or 1 at Day 7 or Discharge from the hospital (whichever is earlier).

If the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) contains zero, pRESET will be considered not significantly different from Solitaire. If the upper bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is less than zero, the proportion of early responders pRESET will be considered significantly lower compared to Solitaire. If the lower bound of the 2-sided 95% confidence interval of the difference (pRESET

minus Solitaire) is greater than zero, the proportion of early responders with pRESET will be considered significantly higher compared to Solitaire.

The results will be presented in Table 14.8.1 entitled *Summary of the Proportion of Early Responders by Randomized Treatment Assignment*. The supportive data for Tables 14.8.1 will be presented in Listing 16.6.1 entitled *Neurologic Status*. This listing will be sorted by clinical site and patient number.

10.6.6. Exploratory Endpoint 6: proportion of patients with all intracranial hemorrhages using the Heidelberg Bleeding classification by randomized study device

The research question for this endpoint is presented below:

Does the 2-sided 95% binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients who experience intracranial hemorrhages contain zero?

The proportion of patients who experience intracranial hemorrhage will be presented using counts, percentages, and the risk difference (pRESET minus Solitaire) with the 2-sided 95% confidence interval of the difference.

If the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) contains zero, pRESET will be considered not significantly different from Solitaire. If the upper bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is less than zero, the proportion of patients with intracranial hemorrhage with pRESET will be considered significantly lower compared to Solitaire. If the lower bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is greater than zero, the proportion of patients with intracranial hemorrhage with pRESET will be considered significantly higher compared to Solitaire.

Results will be presented in Table 14.9.1 entitled *Summary of Intracranial Hemorrhages within 90 days of the Index Stroke*. Results will be supported by listing 16.13.1 entitled *Intracranial Hemorrhages.*

10.6.7. Exploratory Endpoint 7: Stroke Related Mortality at 90 Days After the Index Stroke

The hypothesis is that the proportion of patients stroke-related mortality is not significantly different between the randomized treatment groups.

If the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) contains zero, pRESET will be considered not significantly different from Solitaire. If the upper bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is less than zero, the proportion of patients who experience stroke-related death with pRESET will be considered significantly lower compared to Solitaire. If the lower bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is greater than zero, the proportion of patients who experience stroke-related death with pRESET will be considered significantly higher compared to Solitaire.

The results will be presented in Table 14.10.1 entitled *Stroke Related Mortality by Randomized Treatment Assignment*. The supportive data for Tables 14.10.1 will be presented in Listing 16.8.1 entitled *Mortality Results*. This listing will be sorted by clinical site and patient number.

10.6.8. Exploratory Endpoint 8: Proportion of Patients with Neurological Deterioration at the Time of Discharge or Day 7 (whichever is earlier)

The research question for this endpoint is presented below:

Does the 2-sided 95% binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients classified as having neurological deterioration contain zero?

Neurological deterioration is defined as ≥ 4-point increase in the NIHSS score from the baseline score.

If the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) contains zero, pRESET will be considered not significantly different from Solitaire. If the upper bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is less than zero, the proportion of patients with neurological deterioration with pRESET will be considered significantly lower compared to Solitaire. If the lower bound of the 2-sided 95% confidence interval of the difference (pRESET minus Solitaire) is greater than zero, the proportion of patients with neurological deterioration with pRESET will be considered significantly higher compared to Solitaire.

The results will be presented in Table 14.14.1 entitled *Summary of the Proportion of Patients with Neurological Deterioration by Randomized Treatment Assignment*. The supportive data for Tables 14.10.1 will be presented in Listing 16.6.1 entitled *Neurologic Status*. This listing will be sorted by clinical site and patient number.

10.6.9. Exploratory Endpoint 9: Comparison of the incidence of procedure-related and device-related serious adverse events (PRSAEs and DRSAEs) through 24 (-6/+24) hours post-procedure

The proportion of patients who experience a procedure-related and/or device-related serious adverse events (PRSAEs and DRSAEs) through 24 (-6/+24) hours post-procedure will be presented using counts, percentages, and the risk difference (pRESET minus Solitaire) with the 2-sided 95% confidence interval of the difference. Results will be presented in Table 14.3.9 entitled *Summary of the Incidence of Procedure-Related and Device-Related Serious Adverse Events (PRSAEs and DRSAEs) through 24 (-6/+24) hours Post-Procedure*. Results will be supported by listing 16.16.1 entitled *Serious Adverse Events.*

10.6.10. Analysis of the Barthel Index Scores

The Barthel Index results for each patient 7-10 days post-procedure or discharge, and 90 days post-procedure will be tabulated and presented in Table 14.11.1 entitled *Summary of the Barthel Index by Randomized Treatment Assignment and Time (ITT).*

There are 10 components that create the total score:

- Feeding
- Bathing
- Personal Grooming
- Dressing
- Bowel Control
- Bladder Control
- Toilet Transfers
- Chair/Bed Transfers

- Ambulation
- Stair Climbing
-

The total score will be used in the analysis. Descriptive statistics (number of observations, arithmetic average, standard deviation, median and the range) will be used to summarize the Barthel Index by randomized treatment assignment and observation time. The Barthel Index scores will be compared between the randomized device groups using a 2-sample (randomized treatment assignment) t-test.

The supportive data for Table 14.11.1 will be presented in Listings 16.10.1 entitled *Barthel Index*. This listing will be sorted by clinical site and patient number.

10.6.11. Analysis of the Duration of Hospitalization

The duration of hospitalization (days) for treatment of the study procedure for each patient will be tabulated and presented in Table 14.12.1 entitled *Summary of the Duration of Hospitalization for Treatment of the Study Procedure (ITT)*. Descriptive statistics (number of observations, arithmetic average, standard deviation, median and the range) will be used to summarize the number of days of hospitalization by randomized treatment assignment. The mean duration of hospitalization will be compared between the randomized device groups using a 2-sample (randomized treatment assignment) t-test.

The supportive data for Table 14.12.1 will be presented in Listings 16.11.1 entitled *Hospital Admission for the Current Ischemic Stroke*. This listing will be sorted by clinical site and patient number.

10.6.12. Analysis of the Rate of Hospital Readmissions for Stroke

The number of readmissions for each patient for stroke within 90 days of the index stroke will be tabulated and presented in Table 14.13.1 entitled *Summary of Hospital Readmissions for Stroke (ITT)*. The total intra-patient number of readmissions will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, and range (*i.e.*, minimum and maximum values). The number of readmissions will be compared between the randomized treatment groups using a Wilcoxon 2-sample test.

The supportive data for Table 14.13.1 will be presented in Listing 16.12.1 entitled *Hospital Readmission for Stroke*. This listing will be sorted by clinical site and patient number.

10.7. Follow-up Information and Imaging

A summary of the follow-up imaging will be presented for the following factors. The observational time points will follow the nominal visit schedule.

- NIH Stroke Scale
- mRS
- Barthel Index
- Imaging modality was used on the patient
  - CT
  - MRI
  - MRA

  - CTA
  - Perfusion Imaging
- Evidence of new infarct outside the original at-risk territory? (yes, no)

A summary of the results will be presented in Table 14.15.1 entitled *Summary of Follow-up Imaging and Neurological Examinations.* The supportive documentation will be presented in Listing 16.14.1 entitled *Follow-up Imaging and Neurological Examinations*. This listing will be sorted by clinical site and patient number.

11. SAFETY

The following sections describe how the safety results will be analyzed.

11.1. Analysis of the Primary Safety Endpoint

The primary safety endpoint of this study maps to the primary safety objective and addresses the following research question:

Within 24 hours (-8/+12 hours) after the study procedure, is the upper bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) with device-delated or procedure-related sICH below the a priori threshold of 5%?

The hypothesis is that the proportion of patients with sICH is not significantly difference between the randomized treatment groups. The null and alternative hypotheses can be defined mathematically as follows:

- H_o: Treatment with pRESET is inferior to treatment with Solitaire for sICH within 24 hours (-8/+12 hours) after the study procedure based on a non-inferiority margin of 5%.
- H_a: Treatment with pRESET is non-inferior to treatment with Solitaire for sICH within 24 hours (-8/+12 hours) after the study procedure based on a non-inferiority margin of 5%.

If the upper bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in sICH within 24 hours (-8/+12 hours) after the study procedure is numerically less than 5%, pRESET will be considered non-inferior to Solitaire.

Details in the following sections will provide the results for the evaluation of this endpoint.

11.2. Adverse Events

11.2.1. Definition of Adverse Event

An Adverse Event (AE) is defined as any decline away from the patient's baseline health. Any decline from the patient's pre-treatment condition that occurs during the course of the clinical Study, after starting treatment, whether related to the investigational device, the procedure or the disease. Treatment includes all investigative or commercially approved products administered according to the Investigational Plan.

The following information regarding each AE will be obtained: date and time of onset and resolution (duration), intensity (defined below), whether it was serious, any required treatment or action taken, outcome, relationship to the investigational vaccine, and whether the AE caused withdrawal from the study.

Mild: Patient is aware of event or symptom but event/symptom is easily tolerated.

Moderate: Patient experiences sufficient discomfort to interfere with or reduce their usual level of activity.

Severe: Significant impairment of functioning; patient is unable to carry out usual activities.

A procedural complication may constitute an AE if it results in an untoward change from the patient's baseline health.

The physician will categorize the relationship of the adverse event as follows:

Study Disease-related: Event is clearly attributable to underlying disease state with no temporal relationship to the device, treatment or medication.

Procedure/Treatment-related: Event has a strong temporal relationship to the procedure or treatment of the device implantation or any user handling.

Device-related: Event has a strong temporal relationship to the device and alternative etiology is less likely.

Device Unknown: Device related but unable to attribute a specific device relationship.

Other: Event has no relationship to the disease, procedure or device.

Unknown: Event relationship is not known or unsure.

11.2.2. Definition of Serious Adverse Event

A Serious Adverse Event (SAE) is an event that leads to death, fetal distress, fetal death or a congenital abnormality or birth defect, and serious deterioration in the health of a patient that resulted in a life-threatening illness or injury such as a permanent impairment of a body structure or a body function, requiring in-patient hospitalization or prolongation of existing hospitalization, results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

11.2.3. Missing and Partial Adverse Event Dates

The recorded dates for adverse events are important for an accurate tabulation of both events and patients, and required for the following:

1. Defining the peri-procedural or post-procedural algorithm.
2. Designation of unique adverse event occurrences recorded intra-patient.

Completely missing or partially missing adverse event dates will be imputed as follows, after due diligence to obtain accurate adverse event information has failed.

If the adverse event start date is completely missing the adverse event will be considered as having occurred during the study unless it can be determined that the adverse event end date occurred prior to the start of the study procedure. If the adverse event end date can be established as prior to the date of the study procedure, the adverse event will be considered as having occurred prior to the start of the study.

If the adverse event start date is partially missing and the partial date is not sufficient to determine if the event occurred after the start of the study, then the adverse event will be considered as having occurred during the study.

11.2.4. Summaries of Adverse Events

All summaries of adverse events will be based on events that occurred during the study. Adverse events will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percentage of patients experiencing adverse events will be summarized by system organ class and preferred term. Summaries by maximum severity and relationship to the study device and procedure will also be provided. Serious adverse events and adverse events leading to discontinuation from the study will be presented by system organ class and preferred term. Results will be presented for each of the following 3 groups

- Patients randomized to the pRESET device
- Patients randomized to the Solitaire device, and
- All randomized patients.

The number and percentage of patients experiencing 1 or more serious adverse events will be presented by preferred term using counts and percentages. The proportion of patients with serious adverse events will be compared between the randomized device groups using a two-tailed Fisher's exact test.

Procedural events are defined as an unintended result, observation, or abnormality which was not associated with any clinical sequelae. All study site reported procedural events will be adjudicated by the CEC. The number and percentage of patients experiencing 1 or more procedural events will be presented by the event description using counts and percentages. The proportion of patients with events will be compared between the randomized device groups using a two-tailed Fisher's exact test.

Technical events are defined as device or accessory malfunctions that are not associated with any clinical sequelae. All study site reported technical events will be adjudicated by the CEC. The number and percentage of patients experiencing 1 or more technical events will be presented by the event description using counts and percentages. The proportion of patients with events will be compared between the randomized device groups using a two-tailed Fisher's exact test.

Table 14.3.1 entitled *Summary of Adverse Events by System Organ Class and Preferred Term* contains the primary presentation of the adverse event data. This table is prepared without regard to causality or relationship to the study procedure or device. Patients will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a patient will only be counted once. The number and percentage of patients experiencing each system organ class and preferred term will be displayed by randomized treatment assignment, independent of the device actually used. System organ classes, and preferred terms within a system organ class will be displayed alphabetically. The

overall adverse event rates will be summarized using counts, percentages, and exact 95% binomial confidence limits and compared using a 2-tailed Fisher's exact test.

All adverse events, both serious and non-serious, and including peri-procedural and post-procedural events, will be assessed for severity or intensity according to the criteria described in the protocol. Table 14.3.2 entitled *Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term with Respect to Maximum Severity* provides the presentation of adverse events with respect to the severity of the event. The number and percentage of patients experiencing adverse events for each body system and preferred term will be displayed by randomized treatment assignment and severity. The probability value to compare the event rates by preferred term and severity between the randomized device groups will be based on the 2-tailed Fisher's exact test.

Table 14.3.3 entitled *Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to the Study Device* provides the presentation of adverse events by relationship to study device. This table will have the same structure as that of Table 14.3.1, however, only those adverse events that were determined to be related to study device will be displayed. Patients with multiple occurrences of the same system organ class or preferred term will be summarized using the event with the strongest relationship to study device. The number and percentage of patients experiencing each system organ class and preferred term will be displayed. The probability value to compare the overall event rates between the randomized device groups will be based on the 2-tailed Fisher's exact test.

Table 14.3.4 entitled *Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to the Study Procedure or Treatment* provides the presentation of adverse events by relationship to study procedure or treatment as defined by the **Procedure/Treatment-related** definition. This table will have the same structure as that of Table 14.3.1, however, only those adverse events that were determined to be **Procedure/Treatment-related** will be displayed. Patients with multiple occurrences of the same system organ class or preferred term will be summarized using the event with the strongest relationship to study device. The number and percentage of patients experiencing each system organ class and preferred term will be displayed. The probability value to compare the overall event rates between the randomized device groups will be based on the 2-tailed Fisher's exact test.

Table 14.3.5 entitled *Summary of Adverse Events by System Organ Class and Preferred Term Leading to Study Discontinuation* displays all adverse events resulting in the completion status defined as premature discontinuation due to an adverse event. This table will have the same structure as Table 14.3.1, however, only those adverse events that led to discontinuation will be displayed. Patients will be counted only once at the system organ class and preferred term level; multiple occurrences of the same preferred term for a patient will be counted only once. The number and percentage of patients experiencing each body system and preferred term event leading to premature discontinuation will be displayed by randomized treatment assignment. The probability value to compare these overall event rates between the randomized device groups will be based on the 2-tailed Fisher's exact test.

Listing 16.15.1 entitled *Adverse Events* provides supportive data for Tables 14.3.1 through 14.3.5 and is sorted by clinical site, patient and relative day to the study procedure.

Adverse event incidence rates by system organ class and preferred term will be summarized for patients who report a serious adverse event in Table 14.3.6 entitled *Summary of Serious Adverse Events by System Organ Class and Preferred Term*. This table constitutes a subset of the events reported in Table 14.3.1. Patients with multiple SAEs will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a patient will be counted only once. The number and percentage of patients experiencing each system organ class and preferred term will be displayed by treatment. The probability value to compare these overall event rates between the randomized device groups will be based on the 2-tailed Fisher's exact test.

Series adverse events considered to be procedure-related and/or device-related will be presented in Table 14.3.7 entitled *Summary of Serious Device and/or Procedure Related Adverse Events by System Organ Class and Preferred Term* will follow the same format as Table 14.3.5, however only the serious adverse events will be considered in the tabulation that meet the following definition:

Procedure-related and device-related serious adverse events (PRSAEs and DRSAEs) through 24 (-6/+24) hours post treatment (time zero) as adjudicated by the clinical events committee, and defined as:
a. Vascular perforation
b. Intramural arterial dissection
c. Embolization to a new territory
d. Access site complication requiring surgical repair or blood transfusion
e. Intra-procedural mortality
f. Device failure (in vivo breakage)
g. Any other complications adjudicated by the CEC to be related to the procedure

Table 14.3.8 entitled *Summary of Serious Adverse Events by System Organ Class and Preferred Term Leading to Study Discontinuation* will follow the same format as Table 14.3.5, however only the serious adverse events will be considered in the tabulation.

Listing 16.16.1 entitled *Serious Adverse Events* constitutes a subset of the data provided in Listing 16.15.1. The format of Listing 16.16.1 will be similar to that of Listing 16.15.1 with the exception that the column indicating whether or not the adverse event was serious will be removed as all adverse events in this listing will be SAEs.

11.3. Concomitant Medications

Concomitant medications refer to all medications taken during the study, including medications continued from the pre-treatment screening period. *Prior medications* refer to all medications that were started and stopped prior to the first treatment with study device and will not be reported as concomitant.

Medications with missing start and stop dates, or having a start date prior to the start of study procedure and missing a stop date, will be counted as concomitant. Partial dates will be handled as follows:

- if the year of the study procedure is ≤ the year of start of concomitant medication AND if the month and day of start of concomitant medication are missing AND if the medication stop date is not prior to the date of the study procedure, then the medication is considered concomitant;

- if the year of the study procedure = the year of start of concomitant medication AND if the month of the study procedure is ≤ the month of start of concomitant medication AND if the day of start of concomitant medication is missing AND if the medication stop date is not prior to date of the study procedure, then the medication is considered concomitant.

A summary of the concomitant medications will be presented in Table 14.16.1 entitled *Summary of Concomitant Medications*, containing a clear declaration regarding the start date of the medication relative to the study procedure. The concomitant medications taken by the safety population will be displayed in Listing 16.17.1 entitled *Concomitant Medications*.

11.4. Urine Pregnancy Test Results

Listing 16.18.1 entitled *Urine Pregnancy Test Results* will be presented by patient. This listing will be sorted by clinical site, patient number and the date and results of the test.

11.5. Deviations

Listing 16.19.1 entitled *Protocol Deviations* will be presented by patient and include all of the information recorded on the deviation form in the CRF. This listing will be sorted by clinical site, patient number and the type of deviation.

12. REFERENCES

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5. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030 (ESCAPE).
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13. TABLE, LISTINGS, AND FIGURES

Refer to the appendix containing the index of tables and listings.

14. ADDITIONAL CONSIDERATIONS

TICI - Adjusted Mean and 95% Confidence Limits on the Literature Rates

Study	Y_C	$\bar{Y}$	$Y_C-\bar{Y}$	$(Y_C-\bar{Y})^2$	$W_C (Y_C-\bar{Y})^2$	W_C^*	$W_C^*Y_C^*$
SWIFT PRIME	0.88	0.731256	0.14874431	0.02212487	20.5325502	54.3834134	47.8574038
ESCAPE	0.72	0.731256	-0.01125569	0.00012669	0.07541102	52.6581618	37.9138765
REVASCAT	0.66	0.731256	-0.07125569	0.00507737	2.33052327	51.3108664	33.8651718
EXTEND 1A	0.86	0.731256	0.12874431	0.0165751	4.81834243	48.1918225	41.4449674
MRCLEAN	0.59	0.731256	-0.14125569	0.01995317	19.2190511	54.5000535	32.1550316
				SUM Q=	46.975878	261.044318	193.236451
$\bar{W}$=	647.23516						
S_W^2=	85984.797			D1=	0		
U=	2482.6611			D2=	0.01731041		
				$\bar{Y}^*$	$SE(\bar{Y}^*)$	LCL	UCL
				0.74024385	0.06189319	0.6189332	0.86155451

Since Q>C-1, an adjustment was made to the mean success rate and the between study standard error has increased to 0.0619. This demonstrates that the upper and lower limits are 0.7402 ±0.1213 (1.96*0.0619). The variability between and within the five studies is 0.12.1 (12.1%) and a margin of equivalence that size or smaller would be appropriate. The non-inferiority margin for this study will be set at -12.1%.

SICH - Adjusted Mean and 95% Confidence Limits on the Literature Rates / Restricted to Studies where the SICH was not reported as zero

Study	Y_C	$\bar{Y}$	$Y_C-\bar{Y}$	$(Y_C-\bar{Y})^2$	$W_C (Y_C-\bar{Y})^2$	W_C^*	$W_C^* Y_C^*$
ESCAPE	0.104	0.048687	0.05531294	0.00305952	3.93997458	417.803883	43.4516038
REVASCAT	0.019	0.048687	-0.02968706	0.00088132	4.87022389	556.205916	10.5679124
MRCLEAN	0.077	0.048687	0.02831294	0.00080162	2.62804928	520.302224	40.0632712
				SUM Q=	11.4382478	1494.31202	94.0827874
$\bar{W}$=	3364.078						
S_W^2=	4496243.1			D1=	0		
U=	5837.1257			D2=	0.00161693		
				$\bar{Y}^*$	$SE(\bar{Y}^*)$	LCL	UCL
				0.0629606	0.02586898	0.0122574	0.11366381

Since Q>C-1, an adjustment was made to the mean success rate and the between study standard error has increased to 0.0259. This demonstrates that the upper and lower limits are 0.0630 ±0.0507 (1.96*0.0259). The variability between and within the three studies is 0.05 (5%). and a margin of equivalence that size or smaller would be appropriate. The non-inferiority margin for this study will be set at 5%.