1.0 Title

ARISE II Statistical Analysis Plan

2.0 Approvals

Function / Role	Printed Name	Signature	Date
Originator / VP Clinical, QA & RA	Mairsíl Claffey	Refer to all copies of page 2 in the attached document.	
Originator / ARISE II Executive Steering Committee Member	Prof. Heinrich Mattle		
Originator / ARISE II Principal Investigator	Prof. Tommy Anderson		
Originator / ARISE II Principal Investigator	Dr. Osama Zaidat		
Originator / ARISE II Statistician	Neil O'Leary		
Originator / ARISE II Statistician	Amanda Reilly		

3.0 Attached Document Details

Document Description	Doc. ID	Rev. #	DCN #	Page Count
ARISE II Statistical Analysis Plan	CWI007	01	830	31 pages

Statistical Analysis Plan

Protocol Title:	ARISE II (Analysis of Revascularization in Ischemic Stroke with EmboTrap®)
Protocol Number:	CIP002 rev 05
Protocol Date:	28th June 2016
SAP Authors:	see approvers
SAP Version Number:	v3.0 – 13th September 2017

CONFIDENTIAL

Approvals

Approved By:

13th Sept 2017

Name: Mairsíl Claffey Date:
VP Quality, Regulatory and Clinical Affairs, Neuravi

Sept. 13, 2017

Name: Prof. Heinrich Mattle Date:
Senior Consultant, Dept. of Neurology, Inselspital,
University of Bern, 3010 Bern, Switzerland

Name: Prof. Tommy Andersson Date:
Karolinska University Hospital and Karolinska Institute
SE-17176, Stockholm, Sweden

Name: Dr. Osama Zaidat Date:
Medical Director, Neuroscience and Stroke Programs,
St Vincent Mercy Medical Center, Toledo, OH 43608

Name: Neil O'Leary Date:
Biostatistician, Clinical Research Facility, Galway

Name: Amanda Reilly Date:
Biostatistician, Clinical Research Facility, Galway

CONFIDENTIAL

Approvals

Approved By:

Name: Mairsíl Claffey Date:
VP Quality, Regulatory and Clinical Affairs, Neuravi

Sept 13, 2017

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Senior Consultant, Dept. of Neurology, Inselspital,
University of Bern, 3010 Bern, Switzerland

Name: Prof. Tommy Andersson Date:
Karolinska University Hospital and Karolinska Institute
SE-17176, Stockholm, Sweden

Name: Dr. Osama Zaidat Date:
Medical Director, Neuroscience and Stroke Programs,
St Vincent Mercy Medical Center, Toledo, OH 43608

13/09/17

Name: Neil O'Leary Date:
Biostatistician, Clinical Research Facility, Galway

13/09/17

Name: Amanda Reilly Date:
Biostatistician, Clinical Research Facility, Galway

CONFIDENTIAL

Approvals

Approved By:

Name: Mairsil Claffey Date:
VP Quality, Regulatory and Clinical Affairs, Neuravi

H Mattle Sept 13, 2017

Name: Prof. Heinrich Mattle Date:
Senior Consultant, Dept. of Neurology, Inselspital,
University of Bern, 3010 Bern, Switzerland

Name: Prof. Tommy Andersson Date:
Karolinska University Hospital and Karolinska Institute
SE-17176, Stockholm, Sweden

9/14/2017

Name: Dr. Osama Zaidat Date:
Medical Director, Neuroscience and Stroke Programs,
St Vincent Mercy Medical Center, Toledo, OH 43608

Name: Neil O'Leary Date:
Biostatistician, Clinical Research Facility, Galway

Name: Amanda Reilly Date:
Biostatistician, Clinical Research Facility, Galway

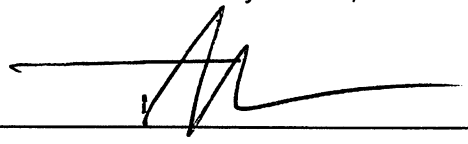
CONFIDENTIAL

Approvals

Approved By:

Name: Mairsíl Claffey Date:
VP Quality, Regulatory and Clinical Affairs, Neuravi

Name: Prof. Heinrich Mattle Date:
Senior Consultant, Dept. of Neurology, Inselspital,
University of Bern, 3010 Bern, Switzerland



17/09/2017

Name: Prof. Tommy Andersson Date:
Karolinska University Hospital and Karolinska Institute
SE-17176, Stockholm, Sweden

Name: Dr. Osama Zaidat Date:
Medical Director, Neuroscience and Stroke Programs,
St Vincent Mercy Medical Center, Toledo, OH 43608

Name: Neil O'Leary Date:
Biostatistician, Clinical Research Facility, Galway

Name: Amanda Reilly Date:
Biostatistician, Clinical Research Facility, Galway

Table of Contents

1 *Revision History*

Revision	Description	Date
1	This SAP is to align with CIP002 rev 05 as submitted to FDA for review	27/07/2017
2	Updated to include Procedural mTICI and Procedural revascularisation endpoints.	22/08/2017
3	Clarifications/edits on: o confidence interval o performance goal notation o type of analysis for secondary outcomes o regional and site level analysis for poolability o missing data on primary endpoint	05/09/2017

2 *Abbreviations and Definitions*

ADE	Adverse Device Effect
AE	Adverse Event
ARISE	Analysis of Revascularization in Ischemic Stroke with EmboTrap
ASPECTS	Alberta Stroke program early CT score
CE	Conformité Européene (European Conformity)
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
DSMB	Data Safety Monitoring Board
eCRF	Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IA-tPA	Intra-arterial tissue plasminogen activator
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
IFU	Instructions for Use
ITT	Intention-to-treat
IV	Intravenous
IV-tPA	Intravenous tissue plasminogen activator
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Score
mTICI	modified Thrombolysis in Cerebrovascular Infarction
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Score
pc- ASPECTS	Posterior circulation ASPECTS
PI	Principal Investigator
PG	Performance goal
PRSAE	Procedure Related Serious Adverse Event
PTAE	Pretreatment Adverse Event
SAE	Serious Adverse Event/Experience
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
sICH	Symptomatic Intracerebral Hemorrhage (which includes also intracranial extracerebral bleedings as defined in the protocol)
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TFSO	Time From Stroke Onset
TICI	Thrombolysis in Cerebrovascular Infarction
TIMI	Thrombolysis in Myocardial Infarction
TS	Treated Set
UADE	Unanticipated adverse device effect
US	United States of America

3 *Preface*

Endovascular mechanical revascularization (thrombectomy) is an increasingly used method for intracranial large vessel recanalization in acute ischaemic stroke. Currently, a number of mechanical recanalization devices are in clinical use. First generation devices included the Merci Retriever device. Newer devices based on stent-like technology, referred to as “stentrievers” or “stent- retrievers”, have displaced these first generation thrombectomy devices for recanalization in acute ischemic stroke secondary to large vessel occlusion.

The EmboTrap® Revascularization Device (hereafter referred to as the EmboTrap device) has been developed and CE approved for this indication in Europe. The EmboTrap device is approved for use in the US strictly within the confines of the ARISE II IDE Study. It is indicated for use in the anterior and posterior neurovasculature in vessels such as the internal carotid artery, the M1 and M2 segments of the middle cerebral artery, the vertebral artery, and the basilar artery.

This study is designed to show non-inferiority to devices already approved for use on the US market and thereby supply clinical data in support of a 510k application for regulatory approval in the United States

The structure and content of this statistical analysis plan (SAP) provides sufficient detail to meet all the requirements in accordance with the International Conference on Harmonisation guidance of Statistical Principles in Clinical Trials (ICH E9). All work planned and reported for this SAP will follow internationally accepted guidelines. The following documents were reviewed in the preparation of this SAP:

- Clinical Research Protocol CIP002*
  - rev 03 issued 19th June 2015
  - rev 05 issued 28th June 2016
- Case Report Forms (eCRFs).
- ICH E9 and E3

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

* Note: Patients were only enrolled and treated under two revisions of the ARISE II study protocol; revision 03 and revision 05. The differences affecting data analyses in these versions relate to;

  - Device of a longer length added during the study to provide an additional choice.
  - Amendment of inclusion criterion #10 and exclusion criterion #15.
  - Revision in the definition of rescue therapy.

4 *Purpose of SAP*

The purpose of this SAP is to detail the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol CIP002. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned analyses not identified in this SAP, will be clearly identified in the respective CSR.

5 *Study Objectives and Endpoints*

5.1 Study objectives

The study objective is to examine the recanalization efficacy of the EmboTrap device and its associated performance characteristics and to record associated clinical outcomes in a

manner that facilitates relevant comparison of outputs with that of devices approved in the U.S. for clearing Large Vessel Occlusions.

5.2 Study endpoints

5.2.1 Primary Efficacy endpoint

The primary efficacy endpoint of the study is revascularization measured using modified Thrombolysis in Cerebrovascular Infarction (mTICI inclusive of the 2c rating). Successful achievement of the endpoint is defined as achieving an mTICI score of 2b or greater in the target vessel, following 3 or less passes of the EmboTrap device. The mTICI result will be based on the final angiogram after the total number of EmboTrap passes performed up to the maximum 3 passes allowed as adjudicated by the Core Lab or the final angiogram after attempted recanalization with the EmboTrap Revascularization Device if rescue devices were used.

Use of rescue therapy, prior to taking the primary endpoint angiogram, is a protocol violation and the resultant angiogram outcomes will be considered failures to achieve the primary endpoint irrespective of mTICI score.

In this single arm study physicians were not precluded from using rescue therapy in the patient post completion of the Primary Efficacy imaging angiogram, this is because more than one vessel, or a previously not visible distal occlusion, may require treatment to achieve a patient optimum outcome. If the physician had a preference for using a smaller device to treat the patient in a distal location or in another vessel this was not precluded.

In a randomised study where both devices would be similarly treated in terms of the use of rescue therapy, and the options for rescue therapy are more limited, a different approach may have been appropriate. As ARISE II was conducted over two continents there were a wide range of device options available to European interventionalists. It would not be appropriate to diminish the efficacy rate reported for EmboTrap by moving all scores of 2b achieved within 3 passes to consider them fails if the interventionalist chose to continue to treat the patient with an alternative device in line with the guidance in the study protocol.

The modified TICI (mTICI) result for assessing the primary efficacy endpoint for a subject will be taken from the final core laboratory adjudicated angiographic result with EmboTrap (within 3 passes).

5.2.2 Primary Safety endpoint

The primary safety endpoint will be measured as the confirmed occurrence of Symptomatic Intracerebral hemorrhage (sICH) within 24 hours (-8/+12 hrs) post-procedure, together with any other Serious Adverse Device Effects (excluding those already counted in sICH).

5.2.3 Secondary endpoints

For patients on whom rescue therapy was employed during the procedure, those secondary endpoints related to neurological outcomes observations will be removed from the data set as detailed in the protocol CIP003 rev 05 and these patients excluded from the main analysis of Good clinical outcome (mRS) and Neurological deterioration. This treatment will apply to the following secondary endpoints:

- **Good clinical outcome** – judged to be an mRS score of ≤2 at 90(+/-14) days.
- **Neuralogical deterioration** – defined by an increase of 4 points or more on the NIHSS score, at the 24-hour time point.

Sensitivity analysis will be performed to assess the robustness of results for these two endpoints to variations in how rescue therapy is defined to define the success of failure to reach an endpoint (Section 10.8).

For the statistical analysis of remaining secondary endpoints, rescue therapy will not be a consideration.

- **Procedure Time** – the time from groin puncture to final angiographic result.
- **Time to treat** - the time from angiographic visualization of large vessel occlusion to achievement of ≥mTICI 2b, or if not achieved, final angiogram. The number of passes to get to mTICI 2b or greater flow will also be recorded.
- **Mortality post-procedure** – All procedure-related mortality (i.e. directly traceable to a procedure- related SAE) at Day 7 post-procedure and all-cause mortality at 90(+/-7) days post-procedure.
- **Serious Adverse Device Effect (SADE)** – CEC confirmed that the EmboTrap device caused, or cannot be ruled out as having caused, an effect that has resulted in any of the consequences characteristic of a serious adverse event.
- **Procedure Related Serious Adverse Events (PRSAE)** – CEC confirmed that the interventional procedure caused, or cannot be ruled out as having caused, an effect that has resulted in any of the consequences characteristic of a serious adverse event.
- **Symptomatic ICH (sICH)** – any extravascular blood in the brain or within the cranium associated with clinical deterioration, as defined by an increase of 4 points or more in the NIHSS score, or that leads to death and is identified as the predominant cause of the neurologic deterioration [3]. For the purpose of data analysis, subjects with sICH identified through all post–treatment scans up to the 24 hour timepoint (including those performed due to clinical deterioration), will be counted.
- **Evidence of Infarction** – Infarction of a previously uninvolved vascular territory, as evaluated from 24-hour imaging (Computed Tomography (CT)/Magnetic Resonance Imaging (MRI)) by the Angiography Core Lab.

5.3 Other important Procedural data

The procedural success rate will be reported.as follows:

The **overall procedural success rate** of the study is revascularization measured using modified Thrombolysis in Cerebrovascular Infarction (mTICI inclusive of the 2c rating). Successful achievement of procedural success is defined as achieving a mTICI score of 2b or greater, as assessed by the angiographic core laboratory, in the target vessel prior to the end of the procedure irrespective of the means or number of passes to achieve.

Procedural success using the EmboTrap device alone is the revascularization rate measured using modified Thrombolysis in Cerebrovascular Infarction (mTICI inclusive of the 2c rating). Successful achievement of EmboTrap procedural success is defined as angiographic core laboratory confirmation of a mTICI score of 2b or greater in the target vessel on the last pass of EmboTrap without rescue therapy.

5.4 Source of Endpoint data and Derived variables

All endpoint data are taken from the finally monitored data collected through the eCRF or in the case of safety endpoints as adjudicated by Clinical Events Committee and imaging endpoints as adjudicated by the core laboratory.

The primary efficacy endpoint of modified Thrombolysis in Cerebrovascular Infarction (mTICI inclusive of the 2c rating) will be extracted from the data provided by Imaging Core Laboratory Intrinsic imaging following all adjudications being completed in the Imaging consensus section of the eCRF.

Results recorded as TICI 2b, TICI 2c or TICI 3 , following 3 or less passes of the EmboTrap device, and without the use of rescue therapy, prior to taking the assessment angiogram (as defined in CIP002 rev 05) in the patient will be treated as having successfully achieved the primary endpoint. Results recorded as TICI 0, TICI 1 or TICI 2a will be treated as failures to achieve the primary endpoint.

The numerator used to calculate the primary safety endpoint will be calculated by summing the recorded occurrence of Symptomatic Intracerebral haemorrhage (sICH) within 24 hours (-8/+12 hrs) post-procedure, together with any Serious Adverse Device Effects (excluding those already counted in sICH) occurring.

A good clinical outcome will be judged to be an mRS score of ≤2 at 90(+/-14) days (mRS score range 0-6). Any subject recorded as having a score of 0, 1 or 2 at this timepoint will have successfully met the endpoint. Subject scores of 3 – 6 are considered fails.

Procedure Time will be derived by calculating the time from when the groin was punctured until the acquisition time for the final post treatment confirmation of angiography result (i.e. the time from groin puncture to visualization/acquisition of the final angiographic result).

Time to Treat will be derived by calculating the time between the last time recorded for angiographic confirmation of the large vessel occlusion and the first time TICI 2b or greater was recorded angiographically, or if TICI 2b or greater was not achieved, the time of last angiographic acquisition.

Other sources of endpoint data are:

- All procedure-related mortality at day 7 post-procedure
- All-cause mortality at 90(+/-14) days post-procedure.
- Serious Adverse Device Effects (SADE).
- Procedure Related Serious Adverse Events (PRSAE).
- Symptomatic ICH (sICH).
- Neurological deterioration – defined by an increase of 4 points or more on the NIHSS, at the 24-hour time point.
- Evidence of Infarction of a previously uninvolved vascular territory, as evaluated from 24-hour imaging (CT/MRI).

A summary of all endpoints and the relevant outcome variables are listed in Table 1.

Table 1: Summary of endpoints and relevant outcomes

	Outcomes	Variable type	Notes
Primary Efficacy	mTICI	Binary	1. Value 1 = TICI 2b, TICI 2c or TICI 3 (favourable) achieved in the final Embotrap pass within 3 passes. 2. Value 0 = TICI 0, TICI 1 or TICI 2a (adverse) 3. All patients treated with Rescue therapy prior to taking of endpoint assessment angiogram count as fails.=0
Primary Safety	Symptomatic ICH (sICH) + Serious Adverse Device (SADE)	Binary	1. Occurrence of either (count only 1 per subject) 2. Within 24 hours (-8/+12 hrs) 3. Values: 1 = favourable, 0 = adverse
Secondary	Good clinical outcome	Binary	1. Judged to be an mRS score of ≤2 at 90(+/-14) days 2. Values 1 = favourable, 0 = adverse 3. Values for patients in whom rescue therapy was used will be excluded from the primary analysis 4.
	Procedure Time	Continuous (positive)	1. Defined as the time from groin puncture to visualization of the final angiographic result 2. Recorded in minutes. 3. No censoring of times 4. Lower value is more favourable
	Time to treat		1. Defined as the time from angiographic visualization of large vessel occlusion to achievement of ≥mTICI 2b, or if not achieved, final angiogram. 2. Recorded in minutes. 3. No censoring of times 4. Lower value is more favourable
	All procedure-related mortality at day 7 post-procedure	Binary	Values: 1 = favourable, 0 = adverse
	All-cause mortality at 90 (+/-14) days post-procedure	Binary	Values: 1 =favourable, 0 = adverse
	Serious Adverse Device Effect (SADE)	Binary	1. The occurrence of any SADE in each patient. 2. Measured across 24 hours post-treatment. 3. Values 1 = favourable, 0 = adverse
	Procedure Related Serious Adverse Events (PRSAE)	Count	1. The number of PRSAEs (count) in each patient. 2. Lower value is more favourable
	Symptomatic ICH (sICH)	Binary	Values: 1 = favourable, 0 = adverse
	Neurological deterioration	Binary	1. Defined by an increase of 4 points or more on the NIHSS score, at the 24-hour time point 2. Values: 1 = favourable, 0 = adverse

	Outcomes	Variable type	Notes
			3. Values for patients in whom rescue therapy was used will be excluded from the primary analysis.
	Embolization to new territory (ENT)	Binary	1. Evaluated from Procedure Angiogram by core laboratory 2. Presence of ENT 3. Values: 1=absent, 0=present
	Evidence of Infarction of a previously uninvolved vascular territory	Binary	1. Evaluated from 24-hour imaging (CT/MRI) by the core laboratory 2. Presence of infarct in a vascular territory that was not involved or expected in the infarct to be treated 3. Values: 1=absent, 0=present
Procedural outcome data	mTICI	Binary	1. Value 1 = TICI 2b, TICI 2c or TICI 3 (favourable) 2. Value 0 = TICI 0, TICI 1 or TICI 2a (adverse)
Procedural outcome using only EmboTrap	mTICI	Binary	1. Value 1 = TICI 2b, TICI 2c or TICI 3 (favourable) using only EmboTrap and no other devices. 2. Value 0 = TICI 0, TICI 1 or TICI 2a (adverse) 3. All patients treated with rescue therapy will count as a fail

6 *Study Methods*

6.1 General Study design and Plan

The study is an open label, single arm study intended to generate a measure of the performance of EmboTrap for clearing and retrieving clots from large vessels causing strokes which can then be compared with a prespecified performance goal.

The study will use core laboratory adjudication to examine the recanalization efficacy of the EmboTrap device in a manner that facilitates relevant comparison of efficacy with a meta-analysis derived composite Performance Goal endpoint based on devices cleared by FDA in the U.S. for unblocking Large Vessel Occlusions. The availability of published core laboratory adjudicated data for a similar population provides an appropriate historical basis to test the hypothesis. Hence, using a single arm study makes efficient use of the available cohort size.

Table 2: Summary of data requirements per study time points

Study Requirement	Screening	Procedure	Post Procedure			
	Within 8 hrs. of onset of stroke	Time 0	24 Hours (-8 to +12 hours)	72 Hours (± 12 hours)	7 Day (168 Hours) or at Discharge	90 Days (± 14 days)
Informed consent	X(1)					
Pregnancy test	X(2)					
NIHSS Score	X(5)		X		X(3)	X
Modified Rankin Scale (mRS)	X					X
Medical history	X					
Physical examination	X				X(3)	
Blood Pressure and Pulse	X					
Assess/confirm study eligibility	X					
CT or MRI	X		X			
Angiography	X(6)	X(7)				
Hemoglobin and Platelet Count	X					
Serum Glucose	X					
Serum Creatinine or GFR	X					
International normalized ratio (INR), activated partial thromboplastin time (APTT)	X					
Mechanical thrombectomy procedure (EmboTrap as well as any rescue devices)		X				
Concomitant medications	X				X(3)	
Record adverse events	X(4)	X	X	X(8)	X(3)	X

(1) Patient or Legally Authorized Representative must sign informed consent prior to screening specific tests which are beyond the local standard of care.
(2) For females of childbearing potential, subjects must have a documented negative pregnancy test prior to device insertion except in the case of local regulations and ethic committee approvals requiring consent post the emergency situation.
(3) To be performed at 168 Hours (+/- 12 hrs) or at discharge (whichever occurs first).
(4) Record all adverse events from the time of signature of the ICF.
(5) Perform prior to angiography.
(6) Perform just prior to mechanical thrombectomy in order to verify the angiographic inclusion/exclusion criteria are met.
(7) Perform angiography after every EmboTrap device pass, at the final EmboTrap device use, after each rescue therapy device pass. Obtain a final angiogram at the end of the interventional procedure.
(8) Follow up at 72 hours is exclusively for adverse events in the consented but not included patients where they were not enrolled because they did not meet the angiographic inclusion or exclusion criteria.

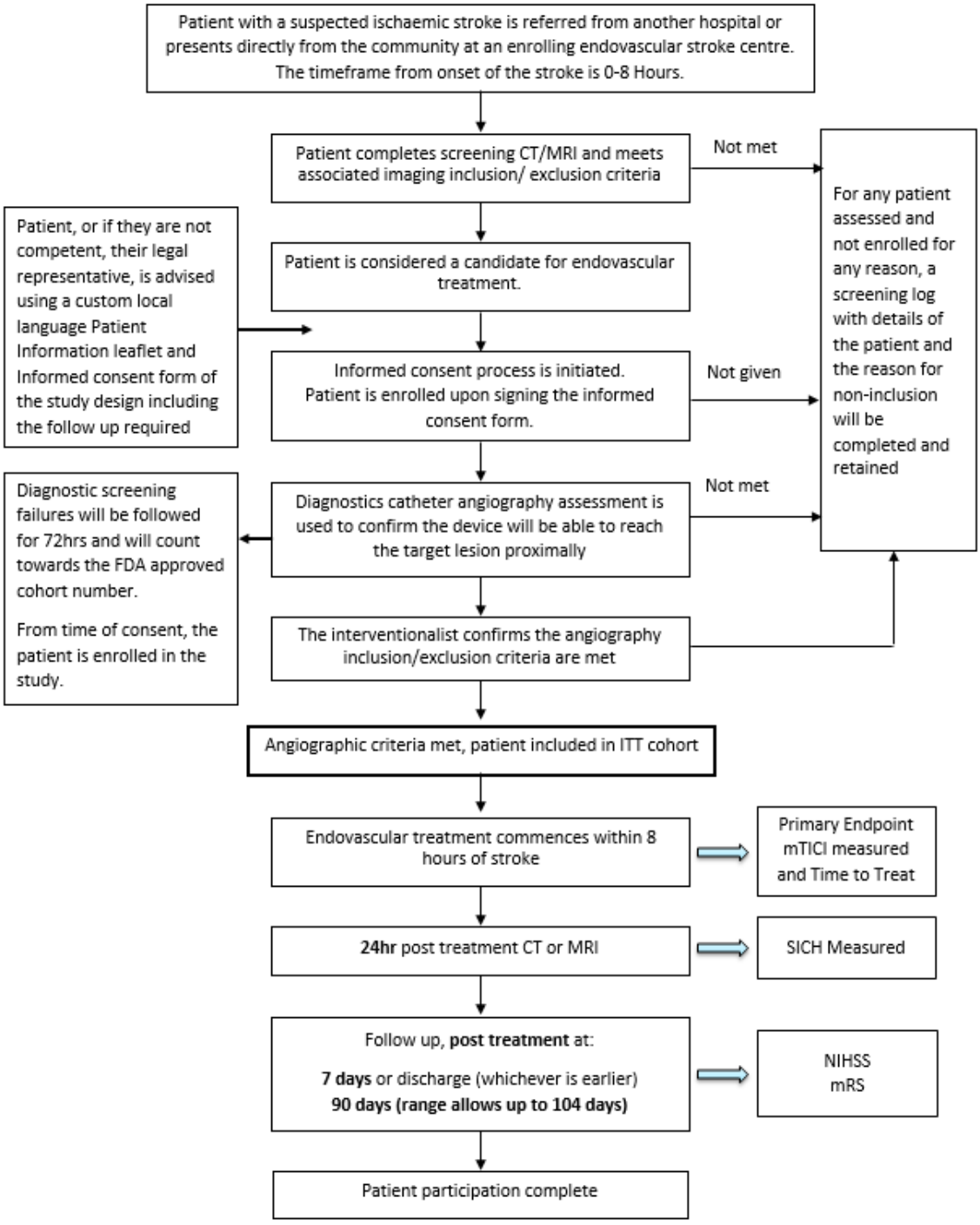


Figure 1: Study flow chart

FDA Approved Cohort number as described in this diagram is the number of US patients (140) FDA approval letter G140253/S004 allowed to be treated in the US under this IDE.

6.2 General Study Population

All consecutive patients presenting for acute ischemic stroke treatment and eligible for the study will be enrolled unless otherwise set out by the clinical site in advance of patient assessment. This could be the case where the site is unable to complete the informed consent process, or where the clinical centre is enrolling stroke patients in multiple studies and has set up a systematic method to enrol presenting patients across studies. Eligibility will be based on the inclusion and exclusion criteria.

6.3 Angiographic Screen Failures

The final inclusion criterion (no. 11) of the protocol is "The patient is indicated for neurothrombectomy treatment by the interventionalist and it is confirmed by diagnostic angiography that the device will be able to reach the target lesion proximally" so that, for this single arm study, angiographic imaging on the table was the final point of confirmation of suitability for patient inclusion. Patients not treated at this point were screen failures, did not receive any Mechanical thrombectomy intervention and based on a request by FDA were followed for 72 hours but not included in the data analyses on device performance.

7 Sample Size

The null hypothesis is that the EmboTrap device performance i.e. revascularization rate (proportion of TICI grades of 2b, 2c or 3), is less than or equal to a non-inferiority limit of 0.56. The alternative hypothesis is that the EmboTrap device achieves a better higher proportion of revascularization than this non-inferiority limit.

The non-inferiority limit is a pre agreed performance goal (PG) for this single arm study and was calculated using a Bayesian Hierarchical Random Effects Meta- Analysis of all the device results in the TREVO 2 and SWIFT studies [1, 2].

A log-normal model was used to model the performance of 3 previous devices, with a logit-link function and normally distributed random study effects for studies and for arms within studies were included on the linear predictor function. Treating only patients from within each study (TREVO 2 and SWIFT) and within each arm as exchangeable with uniform prior on the random effect variances is equivalent to a down- weighting of the Merci device data by 0.75.

An evaluable sample size of 176 revascularization results is needed in order to have at least 90% power to demonstrate non-inferiority against a PG non-inferiority limit (NL) of 0.56, based on a one-sided exact test for a binomial proportion at the 0.025 significance level and assuming that the proportion of adjudicated successes with the EmboTrap device is 0.68.

The estimate of device success rate used above was based on early clinical in vivo experience with the EmboTrap device in an open case series of the CE-marked product across five European centers. The TICI 2b or greater rating achieved was reported by interventionalists at over 74%. It is expected that adjudication may reduce any self-reported adjudication as was the case in both the TREVO 2 and SWIFT studies [1, 2]. 68%was a conservative EmboTrap performance estimate and should ensure the study is large enough to accurately test the endpoint. It is lower than the early experience self-reported rate by 6%.

In the years since the study was initially designed, the self-reported rate of TICI for EmboTrap is generally higher. It is assumed that revascularization outcomes are marginally independent of each other such that no clinical site effect needs to be accounted for which would increase the standard error of any proportion estimate. This assumption will be assessed as described in Section 13.3. The evaluable sample of 176 in the ARISE II trial will be representative of the population of interest and the revascularization results are independent of each other.

7.1 Missing and Censored Data

An extra 30% to the required evaluable patient cohort number is included to bring the total cohort to 228. Missing data will be examined, and the reasons will be investigated and reported.

Missing data for the primary endpoint might be expected in the case of patients eligible for treatment (ITT) but receiving no treatment and thus would have no angiography during procedure from which to make a determination of mTICI. For the primary efficacy outcome, a simple sensitivity analysis of the ITT population will be carried out to assess the robustness

of the conclusions on this endpoint to missing data (see Section 10.3). No missing data is expected for the primary safety outcome and no imputation will be performed for missing data on secondary outcomes. Results measured outside the protocol prescribed time windows, will be treated as missing data.

8 *Timing of analyses*

8.1 Interim analyses

There are no planned interim analyses for this study.

8.2 Final analyses

All final analyses identified in this SAP will be performed after the last patient has completed the study. Before carrying out the analyses, the data management team is responsible for the database cleaning process to ensure the integrity of the analyses. No database may be locked or analyses completed until the SAP has been approved and the database will be locked prior to the initiation of the analysis. Key statistics and study results will be made available following database lock and prior to completion of the final Clinical Study Report (CSR).

Any post-hoc exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR.

9 *Analysis populations*

The primary efficacy endpoint will be examined for the following cohorts, An Intention to Treat cohort, a modified Intention To Treat cohort created to select a data set relevant to FDA lytic labelling constraints relevant at the time of study execution, a Per Protocol cohort, and a Treated Set cohort, which mirrors the protocol, and excludes any violations. The primary population for test will be the ITT.

9.1 Intention to Treat

Intention to Treat (ITT): Will include all patients who meet all angiographic eligibility criteria.

- The primary analysis for the primary efficacy endpoint will be performed on subjects in the ITT cohort with non-missing mTICI assessments.
- The primary safety endpoint analysis will be performed in the subset of treated subjects in the ITT cohort.
- Analyses on the secondary endpoints of Good Clinical Outcome and Neurological Deterioration will be performed in the subset of treated subjects in the ITT cohort with non-missing outcomes in whom rescue therapy was not employed.
- Analyses of other secondary endpoints will be performed in the subset of treated subjects in the ITT cohort with non-missing outcomes
- All specified subgroup analyses.

9.2 Modified Intention to Treat

Modified Intention to Treat (mITT): Prior to study initiation, during study design discussion, FDA indicated interest in results for patients where, if IV-tPA had been administered, it had been shown to fail prior to the introduction of the device. Neuravi considered that using this as an inclusion criterion could be potentially detrimental to the welfare of patients. Hence, it was determined that while no stipulation on waiting to confirm that IV-tPA had failed would be included in the protocol, Neuravi would remove these data after the fact so that data exclusive to patients where IV-tPA has failed or was contraindicated could be

reviewed. There was agreement that failure of IV-tPA would be defined as angiographic evidence of persistent target vessel occlusion, one hour or more after the initiation of IV-tPA therapy.

Accordingly, the mITT cohort is defined to reflect the lytic regime used in the TREVO 2 and SWIFT studies. The mITT cohort will include all patients in the ITT cohort with the exception of those patients in whom less than an hour elapsed between time of initial IV-tPA administration and last pre device use angiography image confirming continued presence of the clot. In order to provide additional context to the results observed in the ITT cohort,

- The analysis for the primary efficacy endpoint will be repeated on subjects in the mITT cohort with non-missing mTICI assessments.
- The analysis for the primary safety endpoint analysis will be repeated in the subset of treated subjects in the mITT cohort.
- Analyses on the secondary endpoints of Good Clinical Outcome and Neurological Deterioration will be repeated in the subset of treated subjects with non-missing outcomes in the mITT cohort in whom rescue therapy was not employed.
- Analyses of other secondary endpoints will be repeated in the subset of treated subjects in the mITT cohort with non-missing outcomes.

9.3 Per Protocol

Per Protocol (PP): Defines a cohort of subjects who meet all eligibility criteria and are treated with the Embotrap device. Patients with protocol violations will be excluded from analysis.

In order to provide additional context to the results observed in the ITT cohort,

- The analysis of the primary efficacy endpoint will be repeated on patients in the PP cohort with non-missing mTICI assessments.
- The analysis of the primary safety endpoint will be repeated on patients in the PP cohort.

9.4 Treated Set

Treated Set (TS): Defines a cohort of subjects who are treated with the EmboTrap device regardless of study eligibility. In order to provide additional context to the results observed in the ITT cohort,

- The analysis of the primary efficacy endpoint will be repeated on patients in the TS set with non-missing mTICI assessments.
- The analysis of the primary safety endpoint will be repeated on patients in the TS set.

10 *General issues for Statistical Analysis*

10.1 Software used for the analysis

All Primary and secondary statistical analyses will be validated by an independent statistician, or using independent software (R, SAS, SPSS, Minitab or Stata). All of the code generated will be kept by both the study statistician and the independent statistician.

10.2 Confidence intervals

All confidence intervals reported for binary variables will be Wilson exact binomial confidence intervals and for continuous variables will be based on a normal distribution assumption for the parameter of interest.

10.3 Methods for Withdrawals, Missing Data, and Outliers

The proportions and causes of missing data for each outcome will be reported. Due to the nature of the data, follow-up schedule and the patient cohort, it is expected that the amount of missing data in the primary and secondary endpoints will be minimal.

For the primary efficacy and outcome, a simple sensitivity of the primary ITT analysis will be carried out by imputing the proportions of success within those participants with a missing outcome (missing mTICI score). This will be done across a range of proportions from 0 to 1 in a "tipping point analysis" [3, 4] for assessing of the robustness of the conclusions on the primary endpoint to missing data. For the secondary outcomes of Good Clinical Outcome and Neurological Deterioration, best and worst case scenario analyses will be performed by treating patients with missing outcomes as successes and failures, respectively.

10.4 Data transformations

Due to the nature of the analysis of the primary and secondary endpoints, it is not expected that any of the data will have to be transformed.

10.5 Multicentre Studies

This is a multi-center clinical study, with standardization of subject enrolment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms.

Given the nature of the intervention, patients from different centers are assumed to be exchangeable. An exploratory analysis will estimate the variation in the primary outcome between centers, adjusting for the different case-mix of patients, though the precision of this estimate is expected to be low.

10.6 Multiple Testing

Since the primary analysis for performance is based only on one endpoint (i.e. revascularization based on the mTICI score), no multiple comparisons will be necessary.

10.7 Planned Subgroups, Interactions, and Covariates

Subgroup analyses will be performed within the ITT population and the TS on outcomes specific to each subgroup analysis. A summary of the proportions of subjects, along with their 95% confidence intervals, within each subgroup for both the primary efficacy outcome and the primary safety outcome, will be reported. Secondary endpoints (see 5.2.3) will be examined descriptively across these subgroups where relevant to further advance the safety and efficacy profile of the device.

A listing of all subgroup analyses to be carried out is provided below with the outcomes listed for each subgroup analysis:

Table 3: Subgroup analysis listing

Analysis	Outcomes	Notes
Males vs. Females	• Primary efficacy • Primary safety	
Compare results for the 21mm length devices to those associated with 33mm devices	• Primary efficacy • Primary safety • Good clinical outcome (mRS)	See 13.4.1

Analysis	Outcomes	Notes
Compare outcomes from the product codes (ET 008 & ET 007) vs. (ET 008-21 & ET-007-21) vs. (ET 008-33& ET 007-21)	• Primary efficacy • Primary safety • Adverse Effects	See 13.4.2
Specific vascular location of the occlusion (i.e. proximal M1/ distal M1 /M2, etc.)	Primary efficacy	Locations to be grouped as follows: • ICA • ICA Terminus (L or T-type) • MCA M1 • MCA M2 • Vertebral • Basilar
Compare use of a balloon guide vs. no balloon guide	Primary efficacy	
Compare use of an intermediate catheter vs. no intermediate catheter	Primary efficacy	
Compare outcomes of patients recruited under revision 03 (issued 19th June 2015) to those under revision 05 (issued 28th June 2016)	Primary efficacy	See 13.4.3
Patients with severe hypertension at enrolment (defined as patient with either SBP>220 mmHg or DBP>120 mmHg) compared to those without.	Primary efficacy	

Demographic and baseline characteristics, procedural information, and clinical outcomes (efficacy and safety) will also be summarized.

10.8 Sensitivity Analysis

A set of sensitivity analyses will be carried out to assess the robustness of conclusions to varying definitions of the target population, definitions of endpoints, and treatment of missing data. These are listed below, along with the relevant outcome to be analysed for each sensitivity analysis. Analyses will report summary parameters (mean or proportion) along with the 95% confidence interval for each.

Analysis will follow the procedure of 10.7 and are listed in the table below.

Table 4: Sensitivity analysis listing

Analysis	Outcomes	Notes
Re-definition of outcomes under rescue therapy	• Primary efficacy • Good clinical outcome (mRS) • Neurological deterioration	Re-analysis of outcomes treating observations with rescue therapy as: 1. observed and, 2. for the secondary outcomes; Clinical outcome and Neurological deterioration, as failure to achieve success
Exclusion of rescue therapy population	Primary efficacy	Re-analysis only on participants not having rescue therapy
Treated Set	Primary efficacy	Re-analysis of outcome using different population according to eligibility criteria (See 9.1)
mITT analysis	Primary efficacy	Re-analysis of outcome using different population according to eligibility criteria (See 9.3)

Analysis	Outcomes	Notes
Redefinition of rescue therapy	Primary efficacy	Re-analysis of outcome given wider definition of rescue therapy to include use of all thrombolytic drugs

10.9 Derived and Computed Variables

The following derived and computed variables have been initially identified. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the code that creates analysis files.

1. Primary safety endpoint:

Rate for subject i: $sICH_i + (SADE_i - SADE_{sICH(i)})$, where:

$sICH_i$ = the number of occurrences subject 'i' has of Symptomatic Intracerebral hemorrhage (sICH) within 24 hours (-8/+12 hrs) post-procedure

$SADE_i$ = any other Serious Adverse Device Effects subject 'i' has

$SADE_{sICH(i)}$ = Serious Adverse Device Effects subject 'i' has which are already counted in $sICH_i$

2. Procedure Time – derived by calculating the time from when the groin was punctured until the acquisition time for the final post treatment confirmation of result angiography (i.e. the time from groin puncture to acquisition of the final angiographic images).

$\text{Time}_{\text{final post-treatment visualization of final angiography result}} - \text{Time}_{\text{groin puncture}}$

3. Time to treat - derived by calculating the time from angiographic visualization of the large vessel occlusion to the first time TICI 2b or greater was recorded angiographically, or if TICI 2b or greater was not achieved, the time of last angiographic result.

If ≥mTICI 2b achieved:
$\text{Time}_{\geq\text{mTICI 2b achieved}} - \text{Time}_{\text{min(time of angiographic visualization of the large vessel occlusion)}}$

If ≥mTICI 2b not achieved:
$\text{Time}_{\text{max(time of angiographic result)}} - \text{Time}_{\text{min(time of angiographic visualization of the large vessel occlusion)}}$

4. Modified Intention to Treat population:

Only patients who are contra-indicated for IV-tPA or in whom IV-tPA has failed will be included (Failure of IV-tPA is defined as angiographic evidence of persistent target vessel occlusion, one hour or more after the initiation of IV-tPA therapy).
This is derived by calculating the difference between the time of the angiography confirming occlusion before first pass and the time of IV-tPA initiation.

$\text{Time}_{\text{angiography confirming occlusion before first pass}} - \text{Time}_{\text{IV-tPA initiated}}$

11 *Study Subjects*

11.1 Subject Disposition

Different variables from the eCRF will be considered to determine the number of patients who reached the various stages of the study, and those who dropped out and for what reasons. These variables will be:

- Date of Informed Consent (Consent form)
- Date of Admission to study/treatment hospital (Pre-procedure form)
- Date of first slice/imaging (Pre-procedure form)
- Date of Endovascular treatment (Procedure form)
- Date of 24 hour post-treatment assessment (24 Hrs Post-Procedure form)
- For angiography screen failures, Date of 72 hour post-treatment assessment (72 Hours Follow-up form)
- Date of 7 day follow-up (Discharge/ 7 Days Post-Procedure form)
- Date of discharge (Discharge/ 7 Days Post-Procedure form)
- Date of 90 day follow-up (90 Days Follow-up form)
- Date of Scan (Imaging Adjudication form)
- Date of EOS Evaluation (End of Study form)
- Date of Death (General form / CEC form)

Corresponding summaries will be presented as the number and percentage of patients who reached each stage of the study, with a graphical display plotting running totals reaching each stage over time.

11.2 Protocol Deviations

A protocol violation is defined as an event that resulted in an increased risk to a subject or others; affected the right, safety or welfare of a subject; or affected the integrity of the study. Protocol violations include, but are not limited to:

- Failure to obtain informed consent prior to patient enrolment
- Enrolled patient did not meet the inclusion/exclusion criteria
- Source data permanently lost
- Introduction of rescue therapy prior to attempting revascularization with EmboTrap for three passes.

Any other events that do not comply with the requirements of the protocol will be considered protocol deviations. Protocol deviations include, but are not limited to:

- Incorrect version of the informed consent form used
- Patient did not attend follow-up visit or follow-up visit was outside the required window

In the case that any violations or deviations occur, a summary of the total number and proportions of each type along with a brief explanation will be presented in the clinical study report.

11.3 Inclusion and Exclusion Criteria

A listing will be generated showing the number and percentage of subjects that fulfilled the inclusion and exclusion criteria listed in sections 6.2 and 6.3 of the CIP002 rev 05.

12 Demographic and Baseline variables

12.1 Demographics

The following will be considered demographic variables, and will be presented in a summary table as follows:

- Age (mean (standard deviation))
- Sex (male/female; n, %)
- Ethnicity (Hispanic or Latino; n, %)
- Race (per category; n, %)

12.2 Prior and Concurrent medications

Prior and Concurrent medications are recorded in the Concomitant Medications Log on the General form of the eCRF. For each one of the medications, summaries will be provided for the number of times the medication was reported at baseline and during the study period (counts and %).

12.3 Baseline and Screening Conditions

The modified Rankin Scale (mRS) is a scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. At screening, an historical mRS will be obtained from the subject or the subject's caretaker. It is an inclusion criterion that the subject has a pre-ictal mRS score of 0 or 1. One of the secondary endpoints of the study is a good clinical outcome, which is judged to be an mRS score of ≤2 at 90(+/-14) days.

The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used to objectively quantify the impairment severity caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between 0 (normal function) and 4 (highest level of impairment). The maximum and minimum possible scores are 42 and 0, respectively. It is an inclusion criterion that the subject has a NIHSS score of between 8 and 25 (inclusive). One of the secondary endpoints is neurological deterioration, which is defined by an increase of 4 points or more on the NIHSS score, at the 24-hour time point.

All baseline and screening variables, including medical history and current medication are listed below. They will be summarised in a table along with the demographic variables.

- NIHSS Score
  - Mean (standard deviation)
  - median (range)
  - ≤17 (%)
- Pre-stroke modified Rankin Scale
  - Median (range)
  - 2 or better
- Body-mass index
  - Mean (standard deviation)
- Intravenous rt-PA failure (n, %)
- Medical History (n, %, per term)
  - Hypertension
  - Diabetes mellitus
  - Dyslipidaemia
  - Current or ex-smoker
  - Atrial fibrillation
  - Previous MI/ CAD
- Neurological History (n, %, per term)
  - Previous Stroke/ TIA
- Core lab assessed Most proximal occlusion location (n, %, per term)
  - Internal carotid artery
  - M1 middle cerebral artery

- M2 middle cerebral artery
- Posterior circulation
- Other

- Occlusion side (left) (n, %)
- Largest occluded vessel size (mm; mean (standard deviation))
-

13 *Efficacy Analyses*

13.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this prospective, multi-center, open-label study is revascularization measured using modified Thrombolysis in Cerebrovascular Infarction (mTICI inclusive of the 2c rating). The endpoint will be extracted from the data inputted by Imaging Core Laboratory Intrinsic imaging following all adjudications being completed in the Imaging consensus section of the eCRF.

Successful achievement of the endpoint is defined as achieving an mTICI score of 2b or greater in the target vessel, following 3 or less passes of the EmboTrap device and without the use of rescue therapy prior to taking the assessment angiogram (as defined in CIP002 rev 05) in the patient. Use of rescue therapy, prior to taking the primary endpoint angiogram, is a protocol violation and the resultant angiogram outcomes will be considered failures to achieve the primary endpoint irrespective of mTICI score.

The study objective is to investigate the performance of the EmboTrap device ($P_{EmboTrap}$) against a Performance Goal for efficacy (PGefficacy). In order to claim non-inferiority against an efficacy driven PG, the lower bound of a (95%) confidence interval must be shown to be greater than a non-inferiority limit (NL) which is the predetermined PGefficacy.

The PGefficacy has been derived from a meta-analysis of revascularization efficacy rates from approved predicate devices' adjudicated performances as reported in the literature.

The meta-analysis involved a Bayesian hierarchical random effects model with a binomial response and logit link function using the efficacy results of all 3 devices in the TREVO 2 and SWIFT studies [1, 2]. Normally distributed random effects for study and arm within study effect were included on the linear predictor function. Only patients from within each study (TREVO 2 and SWIFT) and within each arm were thus treated as exchangeable. A normal prior on the log-odds centred on 0 and uniform prior for the random effect variances were used.

The test for non-inferiority for performance will be based on a one-sided test (at the 0.025 significance level) for a binomial proportion with hypotheses:

$$H0: P_{EmboTrap} \leq NL \quad \text{versus} \quad H1: P_{EmboTrap} > NL$$

Thus the tested non-inferiority hypothesis will relate to the superiority of the EmboTrap device to a non-inferiority limit.

An equivalent testing procedure is available by using the sample data to calculate a confidence interval for the population proportion ($P_{EmboTrap}$). Demonstrating non-inferiority for efficacy necessitates rejecting the null hypothesis in favour of the alternative hypothesis, in this case based on the lower limit of a 95% confidence interval for a population proportion. The evaluable sample in the ARISE II trial are assumed to be representative of the population of interest and from which participants for the TREVO 2 and SWIFT trials were sampled. It is assumed that revascularization outcomes are independent of each other, such that no clinical site effect needs to be accounted for which would inflate the standard error

and confidence intervals of the proportion estimate. This assumption will be assessed as described in Section 13.3.

Estimates of each population parameter of interest for all other endpoints will be provided using appropriate confidence intervals.

The primary efficacy endpoint will be examined for the ITT population and the mITT population, the per protocol population and the Treated Set (described in Section 9) though the primary analysis will be for the ITT population.

13.2 Primary Safety Endpoint and All Secondary Endpoints

The primary safety endpoint will be the rate of sICH together with SADEs (excluding those already counted in sICH), and will be evaluated descriptively and with an unadjusted 95% confidence interval.

Descriptive statistics and unadjusted 95% confidence intervals for secondary endpoints (listed in Section 5.2.3) without any hypothesis tests, will be examined to further advance the safety and efficacy profile of the device.

A summary of the proportions of subjects receiving each category score on the mTICI scale will be reported. Demographics, baseline characteristics, procedural information, and clinical outcomes (efficacy and safety) will also be summarized.

All other binary endpoints will be summarised as proportions with the Wilson exact binomial confidence interval to allow a statement on the uncertainty of the inferred population proportion be made. Descriptive statistics will be used to summarize the clinical outcome variables collected on all vessels treated in this investigation overall and for each center.

The typical value for each continuous response variables will be estimated using the mean and median, while the variability will be estimated using the range, interquartile range and standard deviation. All categorical variables will be reported as counts and percentages.

Box and bean plots will be generated for each continuous response variable, while bar charts will be generated for each categorical variable.

At study completion, summaries of each clinical outcome variable will include corresponding 95% confidence intervals in order to provide an estimate of the corresponding population means, medians and proportions.

13.3 Analysis of Ability to Pool Data across Regions and Investigational Sites

To present the data from this clinical study in a summary form, a comparison of both primary endpoints (safety and efficacy) across sites and across regions will be completed to determine if the generated data can be pooled. Logistic regression models will be fitted for both endpoints with the inclusion of region and study site within region as fixed effects Likelihood ratio tests for the site and region terms in these models will be performed for each endpoint at an alpha level of 0.15 to assess whether outcomes across sites or regions are homogenous. Sites within region with low enrolment may be combined to aid model convergence. If there is evidence for lack of homogeneity, summary statistics by region and/or site within region will be presented for the corresponding endpoint.

13.4 Other Analyses

13.4.1 Analysis of data for the different lengths of device used

An analysis of the primary outcome will be undertaken by comparing the proportions for those who had the procedure done using a 21mm device to those who had the procedure done using a 33mm device, to determine if there is any evidence of a difference from the length of the device used, or if the data are exchangeable between the two device sizes.

13.4.2 Analysis of data for the different versions of device used

The device used under CIP002 rev 03 from the start of the study were of 21 mm length (Product code ET 008 in the US, and ET 007 in Europe). When the protocol was revised from rev 03 to rev 05, new product codes (ET 008-21 and ET 008-33 in the US; ET-007-021 and ET-007-033 in Europe) were introduced. These were for a 21mm length and a 33mm length of device. The revised 21 mm length device was identical to the earlier product except for the addition of two extra radiopaque markers to aid with fluoroscopic visibility. Therefore, the data for all 21 mm length devices is considered completely exchangeable.

Table 5: Device characteristics

Characteristics	Revascularization Device		
	ET-008	ET-008-521	ET-008-533
Indications for Use	The EmboTrap device is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy are candidates for treatment.	Identical	Identical
Stent Material	Nitinol	Identical	Identical
Stent Diameter	5 mm	Identical	Identical
Stent Working Length	21 mm	Identical	33 mm
Radiopaque Materials	Gold Markers (outer cage) Platinum/Tungsten (proximal/distal coils)	Identical	Identical
Shaft Material	Nitinol Wire with PTFE Coating	Identical	Identical
Shaft Length	190 cm	Identical	Identical
Minimum Microcatheter ID	0.021"	Identical	Identical
Method of Supply	Insertion tool and pre-loaded EmboTrap device are packaged in a protective polypropylene hoop, within a labelled Tyvek pouch and unit carton.	Identical	Identical
Sterilization Method	Ethylene Oxide	Identical	Identical

Below is a summary of the three device types included in the study. For European distribution different codes were used. The devices excluding the packaging are identical.

Table 6: Summary of study devices

Types of Device	United States code	European code	Comparison of the devices U.S. and EU codes
First type 21mm long	ET-008	ET-007	Identical unit except for packaging
21 mm long + marker bands	ET-008-521	ET-007-521	Identical unit except for packaging
33mm long + marker bands	ET-008-533	ET-007-533	Identical unit except for packaging

For the purpose of statistically analysing the devices used the device lot numbers will be extracted from the eCRF database and linked to the size of device used as described in Table 5.

Table 7: Product code per lot number

Device Lot Number recorded in ARISE II EDC	Product Code
15J120AV	ET-007
15K019AV	ET-007
15L068AV	ET-007
15M063AV	ET-007
16A069AV	ET-007
16A074AV	ET-007
16A142AV	ET-007
16B101AV	ET-007
16B147AV	ET-007
16C004AV	ET-007
16C078AV	ET-007
16D132AV	ET-007
16E125AV	ET-007
16E183AV	ET-007
16F064AV	ET-007
16F116AV	ET-007
16G052AV	ET-007-533
16G086AV	ET-007
16H086AV	ET-007
16H140AV	ET-007
16J037AV	ET-007-521
16K074AV	ET-007-521
16J006AV	ET-007-533
16J077AV	ET-007-533
16J100AV	ET-007-533
16J153AV	ET-007-533
16K113AV	ET-007-533
16L054AV	ET-007-533
15G108AV	ET-008
15K151AV	ET-008
16A153AV	ET-008
16D164AV	ET-008
16J036AV	ET-008-521
16K027AV	ET-008-521
16j005av	ET-008-533
16K028AV	ET-008-533
16L094AV	ET-008-533

To assess these assumptions of exchangeability, the proportions of participants reaching successful endpoint by the primary outcome will be compared across three versions of product included in the study.

13.4.3 Analysis of protocol version subjects were enrolled under

Patients were only enrolled and treated under two revisions of the ARISE II study protocol; revision 03 (issued 19th June 2015) and revision 05 (issued 28th June 2016). The differences affecting data analyses in these versions relate to;

- additional length of device added as a choice
- amendment of inclusion criterion #10 and exclusion criterion #15
- revision in the definition of rescue therapy

An extra analysis of the primary outcome will be undertaken to determine if there is any difference between data from subjects enrolled under revision 03 of the protocol and data from those enrolled under revision 05 of the protocol.

14 *Safety Analyses*

14.1 Adverse Events

Any adverse events which occur during or after the procedure (up to the 90 day follow-up) will be recorded in the database and documented in the Clinical Study Report (CSR). Adverse events will be adjudicated as to the relationship to the EmboTrap device, procedure or the disease state as well to the severity of the event. Subgroup analyses of the points described in the synopsis will be completed.

An AE that occurs after the ICF has been signed and before the treatment with the EmboTrap has started is identified as a pretreatment AE (PTAE). An AE that occurs after treatment using EmboTrap has started will be considered a treatment emergent AE (TEAE).

All AEs will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA) Coding of Adverse Events nomenclature. Standardized nomenclature that will be ascertained includes lowest level and preferred MedDRA terms, MedDRA System Organ Class. Adverse Events will be summarised based on their severity and relationship to the treatment (as defined by the treating site), with the relationship categorised as 1) Definite, 2) Probable/Possible and 3) Unlikely. Unrelated adverse events will not be reported. Separate tables will be used to show 1) all adverse events and 2) serious adverse events.

14.2 Deaths, withdrawal, and Serious Adverse Events

14.2.1 Serious Adverse Events and Adverse Device Effects

The analysis of Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADEs) based on the assessment data provided by the Clinical Events Committee will include:

- An overview of the number of SAEs and number of SADEs recorded in the study. Specifically, the number of patients experiencing at least one SAE and/or at least one SADE, along with whether the patient was withdrawn as a result of either the SAE or the SADE. The information will be summarized using counts and percentages

- Summaries of the number of patients experiencing serious adverse events, by preferred term (counts and percentages)

14.2.2 Withdrawal due to Adverse Events

Withdrawals will be summarised as the number and percentage of patients who were withdrawn from the study due to an adverse event or adverse device effect.

14.2.3 Deaths

Deaths will be summarised as the number and percentage of patients who died within the study period.

14.3 Pregnancies

Pregnancy data will be shown in a data listing. No special analysis will be performed on the pregnancy data. Patients are to be discontinued from the study if they become pregnant.

14.4 Post-Procedure Evaluations

NIHSS and mRS data are collected on the Pre-Procedure form, and again on the 90 Days Follow-Up form. Shift tables will be used to show how these scores changed between the baseline and 90 day follow-up visits.

15 *Reporting conventions*

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

16 *References*

1. Saver, Jeffrey L., et al. "Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial." The Lancet 380.9849 (2012): 1241-1249.
2. Nogueira, Raul G., et al. "Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial." The Lancet 380.9849 (2012): 1231-1240.
3. Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. J Biopharm Stat. 2009;19(6):1085-98.
4. Campbell G, Pennello G, Yue L. Missing data in the regulation of medical devices. J Biopharm Stat. 2011;21(2):180-95.

17 *Appendices*

Appendix 1: CIP002 rev 05

Appendix 2: Listing of Tables and Data Listings