CLINICAL STUDY PROTOCOL

Post Marketing **S**tudy of **P**atients to **E**valuate NIMBUS **R**evascularization Effectiveness with Challenging **O**cclusions.

Protocol Number: CNV_2018_01

Version: 2.0

Approval Date: 23 JUL 2020

History of change

Version date	Description
Version 1.0 – 31 OCT 2018	**Original document.**
Version 2.0 – 23 JUL 2020	**Protocol revision.**

CERENOVUS acting through Neuravi Ltd.,

Block 3, Ballybrit Business Park,

Galway, H91 K5YD, Ireland

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LIST OF ABBREVIATED TERMS

AE	Adverse Event
ACA	Anterior Cerebral Artery
ADAPT	A Direct Aspiration First Pass Technique
ADE	Adverse Device Effect
AIS	Acute Ischemic Stroke
ASPECTS	Alberta Stroke program early CT score
BA	Basilar Artery
CA	Competent Authority
CBV	Cerebral Blood Volume
CRF	Case Report Form
CT	Computed Tomography
CTA	Computed Tomography Angiography
DBP	Diastolic Blood Pressure
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EDC	Electronic Data Collection
GCE	Geometric Clot Extractor
GCP	Good Clinical Practice
IC	Informed Consent
ICA	Internal Carotid Artery
ICF	Informed Consent Form
ICH	International Council for Harmonization
IFU	Instructions for Use
IV	Intravenous
IV-tPA	Intravenous tissue plasminogen activator
LVO	Large Vessel Occlusion
MCA	Middle Cerebral Artery
mITT	Modified Intention to Treat
MM	Medical Monitor
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
mTICI	Modified Thrombolysis in Cerebrovascular Infarction
NIHSS	National Institute of Health Stroke Scale
OD	Outer Diameter / Outside Diameter
PI	Principal Investigator
PMCF	Post Market Clinical Follow-Up
PTFE	Polytetrafluoroethylene
RBC	Red Blood Cell
RCT	Randomized Control Trial
rtPA	Recombinant Tissue Plasminogen Activator
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAH	Subarachnoid Hemorrhage
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SDV	Source Data Verification
SOC	Standard of Care
SOP	Standard Operating Procedure
SVS	Susceptibility Vessel Sign
VA	Vertebral Artery
WBC	White Blood Cell

KEY ROLES AND RESPONSIBILITIES

Sponsor:	CERENOVUS acting through Neuravi Ltd. Block 3, Ballybrit Business Park Galway, H91 K5YD Ireland
Contacts:	[redacted]
Principal Investigator:	[redacted]
Medical Monitor/Safety Contact:	[redacted]

PROTOCOL AGREEMENT AND STATEMENT OF COMPLIANCE FORM

STUDY NAME AND NUMBER: SPERO (CNV_2018_01)

STUDY TITLE: Post Marketing Study of Patients to Evaluate NIMBUS Revascularization Effectiveness with Challenging Occlusions.

VERSION NUMBER: 2.0

VERSION DATE: 23 JUL 2020

I have read this protocol and agree to conduct this clinical study in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the study is conducted in accordance with specific provisions of the associated ECs, the current applicable version of ISO 14155, the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable national and regional regulatory requirements, the signed agreement with CERENOVUS, and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

I will fulfill the requirements of Ethics Committee (EC) / Competent Authority (CA), or other oversight committee, to ensure complete and continual oversight of this clinical study. I will use an Informed Consent Document approved by the Sponsor and my reviewing oversight committee.

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events (AEs) as defined in this protocol to the Sponsor and will comply with any adverse event reporting requirements of my reviewing oversight committee. I agree to permit the Sponsor, its authorized representatives, my reviewing EC, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments, and will accept respective revisions or amendments provided by the Sponsor.

Principal Investigator (PI):

Name (PRINT)	**Signature**	**Date**

PROTOCOL SYNOPSIS

Study Title	Post Marketing **S**tudy of **P**atients to **E**valuate NIMBUS **R**evascularization Effectiveness with Challenging **O**cclusions. (Protocol#: CNV_2018_01)	
Short Title	SPERO	
Study Sponsor	CERENOVUS acting through Neuravi Ltd. Block 3, Ballybrit Business Park Galway, H91 K5YD Ireland	
Laboratories	Imaging Core Lab: [redacted] Central Lab for Clot Analysis: [redacted]	
Study Device	CERENOVUS NIMBUS Geometric Clot Extractor, hereafter referred to as NIMBUS	
Indication	To restore blood flow in patients experiencing an acute ischemic stroke due to a large vessel neurovascular occlusion. The Device is designed for use in the anterior and posterior neurovasculature in vessels of diameter 1.5 mm to 5.0 mm, such as the internal carotid artery, the M1 and M2 segments of the middle cerebral artery, the A1 and A2 segments of the anterior cerebral artery, the basilar, the posterior cerebral and the vertebral arteries. The Device should only be used by physicians trained in neurointerventional catheterization and the treatment of ischemic stroke.	
Study Design	This is a prospective, multi-center, single-arm, observational post market study that will consecutively enroll up to 50 subjects treated with NIMBUS at up to 10 sites in Europe. Follow up with subjects will occur over 3 months at 24 hours, and 90 days post procedure.	
Sample Size	Approximately 50 subjects will be consecutively enrolled into the study which will involve treatment with NIMBUS.	
Number of Sites	Approximately 10 clinical sites in the EU	
Study Duration	Start Date: Q4 2018	End Date: Q2 2021
Study procedures	Subjects will have challenging occlusions, with mTICI ≤ 2a post one, or two passes, of another Mechanical Thrombectomy device. Any commercially available Mechanical thrombectomy device (i.e. either aspiration or Stent-retriever other than NIMBUS) may be used during the first and up to two vessel clearance attempts. The physician may use his own discretion on whether to introduce the NIMBUS after one failed vessel clearance attempt, or after two.	

	The NIMBUS must be used no later than the overall third procedural pass for the patient to be eligible. Up to 50 subjects will be treated with the NIMBUS. Once the decision has been made to use NIMBUS, it is used for up to three passes. After the third pass with the NIMBUS, if the physician would like to utilize another device/technique for treatment, they may. Angiographic imaging will be collected per every pass for subsequent review by an independent Imaging Core Lab. Clot will also be collected per every pass for analysis in an independent Central Lab. After the procedure, subjects will be followed for 90 days per the schedule below: 1. Study procedure 2. 24 Hour Follow-up (+/- 8 hrs) 3. 90 Day Follow-up (+/- 14 days)
Primary Objective	The objective of this study is to assess the efficacy of the NIMBUS in a real-world setting in patients where the first one or two passes with another Mechanical thrombectomy therapy have not achieved mTICI 2b or better. The rate of effectiveness achieved will be considered as we design further studies. The study will also evaluate and report on clot characteristics and clinical outcomes.
Primary Endpoint	Successful Revascularization (mTICI ≥ 2b) with NIMBUS as determined by an Independent Core Lab.
Secondary Endpoints	1. Successful Procedural Revascularization (final mTICI ≥ 2b). 2. Excellent Procedural Revascularization (final mTICI ≥ 2c). 3. First Pass Revascularization using Nimbus (mTICI ≥ 2b). 4. Occurrence of Embolization to a New Territory (ENT). 5. Symptomatic Intracerebral Hemorrhage (sICH) at 24 hours specified according to the Heidelberg Bleeding Classification (HBC). 6. 90 Day All-Cause Mortality. 7. Modified Rankin Scale (mRS) of ≤ 2 at 90 days.
Ancillary Endpoints	1. Clot Analysis 2. Hospitalization Analysis
Inclusion Criteria	**All Subjects:** 1. Age ≥ 18 2. The subject or the subject's legally authorized representative has signed and dated an Informed Consent Form. 3. Patient has had one or two passes of another mechanical thrombectomy device without achieving mTICI 2b or better and continues to have angiographic confirmation of a Large Vessel Occlusion (LVO[1]) in the same vessel.

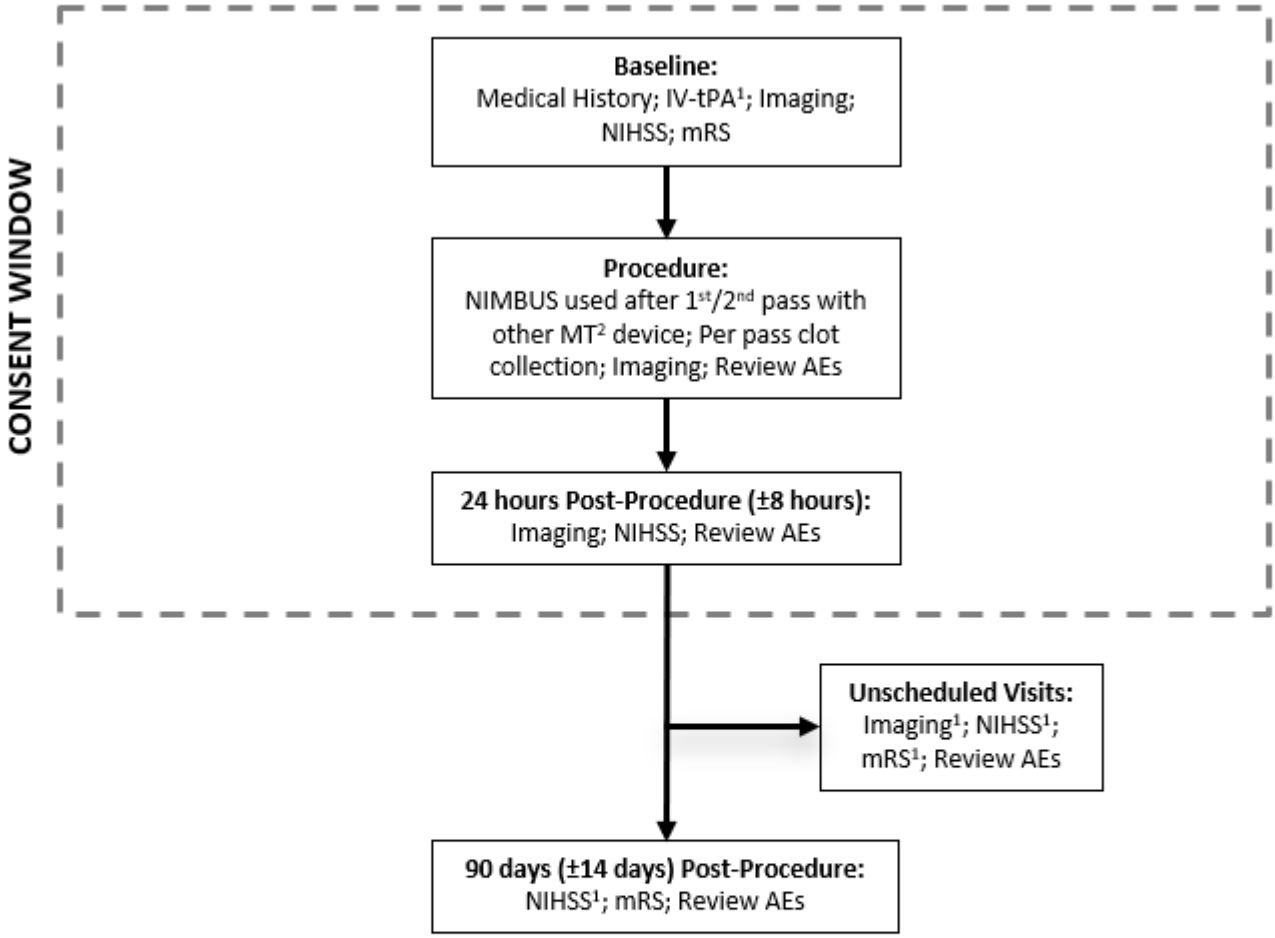
[1] A Large Vessel Occlusion (LVO) is an occlusion in the ICA, MCA, ACA, VA, or BA.

	4. mRS 0-1 prior to this stroke. 5. NIMBUS is used on the second or third overall pass to attempt revascularization.
Exclusion Criteria	1. Currently participating in an investigational (drug, device, etc.) clinical trial that may confound study endpoints. Patients in observational, natural history, and/or epidemiological studies not involving intervention are eligible. 2. Confirmation of positive pregnancy test according to site specific standard of care (e.g. test, verbal communication). 3. All patients with severe hypertension on presentation (SBP > 220 mmHg and/or DBP > 120 mm Hg). All patients, in whom intravenous therapy with blood pressure medications is indicated, with hypertension that remains severe and sustained despite intravenous antihypertensive therapy (SBP >185 mmHg and/ or DBP >110 mmHg). 4. Known cerebral vasculitis. 5. Known cancer with life expectancy less than 12 months. 6. Stenosis, or any occlusion, in a proximal vessel that requires treatment or prevents access to the site of occlusion. 7. Intracranial stenosis that prevents access to the site of occlusion. 8. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) evidence of recent/ fresh hemorrhage on presentation. 9. Baseline computed tomography (CT) or MRI showing mass effect or intracranial tumor (except small meningioma). 10. Evidence of dissection in the extra or intracranial cerebral arteries. 11. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation).
Sample Size and Power Calculation	There is no hypothesis testing for this post-market study. Up to 50 treated subjects are deemed sufficient to evaluate the performance of NIMBUS. These results may be used to inform further studies. Approximately 50 subjects will be consecutively enrolled using commercially available Mechanical Thrombectomy devices during the initial one, or two, Mechanical thrombectomy passes. With an enrolled sample size of 50 and an attrition rate of no more than 10%, the precision (margin of error) for the primary endpoint is anticipated to be around 10.1% based on 2-sided 95% confidence intervals, where the primary endpoint rate is estimated to be 86%. $Margin\ of\ error \approx 1.96 \times SE = 1.96 \times \sqrt{\frac{p(1-p)}{n}} = 1.96 \times \sqrt{\frac{0.86 \times (1-0.86)}{45}} = 10.1\%$ *where SE denotes the standard error and p denotes the proportion of subjects who achieve the primary endpoint.*

Statistical Analysis	Analyses will be presented for approximately 50 subjects treated with NIMBUS. Descriptive summary statistics will be presented for all endpoints. The number and percentage of subjects will be summarized for categorical variables. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, minimum and maximum.

SCHEMATIC OF STUDY DESIGN

Assessments and imaging performed for the study are part of standard of care (SOC) for stroke treatment, and screening can occur without obtaining consent. Informed consent is mandatory and must be obtained before any data is captured in the electronic Case Report Form (eCRF).



Footnote 1: *Optional*
Footnote 2: *Mechanical Thrombectomy*

Note 1. *All thrombectomy subjects for whom a second pass with any thrombectomy device was completed will be recorded in the site screening log.*
Note 2. *Informed Consent may be obtained at any point from imaging confirmation of an Acute Ischemic Stroke through to 7 days post-procedure.*

Figure 1: Schematic of Study Design

SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Table Legend: X = Required; O = Optional, to be collected if performed during standard of care **Assessments**	Enrollment			Follow-up	
	Baseline	Procedure	Post-procedure 24hrs (+/- 8 hrs)	90 Day Follow-up (+/- 14 days)	Unscheduled(6)
ICF		X(2)			
Eligibility Screening		X			
Demographics and Medical History	X				
IV t-PA administration	O				
Imaging (1)	X	X	X		O
NIH Stroke Scale (NIHSS)	X(4)		X(4)	O(4)	O(4)
Modified Rankin Scale (mRS)	X(5)			X(7)	O
Angiography (1)		X			
Review of Applicable Adverse Events (AE)		X	X	X	X
Clot Collection (3)		X			

(1) CT/MR Imaging and angiography will be sent to independent Imaging Core Lab for review.

(2) Due to the emergent nature of AIS, consent may be obtained after the procedure but up to 7 days post-procedure as permitted by the local regulations and EC.

(3) Per pass clot collection to be sent to Central Lab for processing.

(4) If more than one NIHSS was performed during this time period, select the worst (highest) value.

(5) To be evaluated by a qualified evaluator; pre-stroke mRS should reflect the subject's condition just prior to the stroke onset. For example, if the subject was hospitalized during stroke onset, the subject's reason for hospitalization should be taken into account when evaluating the subject's pre-stroke mRS.

(6) Assessments should be completed for unscheduled visits from the time of Discharge up to (but not including) the 90-day Follow-up, where imaging, NIHSS, or mRS is performed as part of stroke management care for the subject.

(7) The 90 day mRS must be performed by a qualified independent evaluator who is not part of the interventional treating team.

1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background

Acute Ischemic Stroke (AIS) affects approximately 613,000 patients in the European Union and 795,000 patients in the United States, annually [1, 2]. IV thrombolytic therapy remains the standard of care for acute ischemic stroke; however, it is not effective in recanalizing large vessel occlusions (LVOs) [3, 4]. The presence of LVO of a major intracranial artery, most commonly the middle cerebral artery (MCA) or internal carotid artery (ICA), is estimated to occur in approximately one-third to one-half of acute ischemic stroke [5].

Occlusion of the large intracranial arteries in ischemic stroke is associated with significant disability and mortality. Timely revascularization of intracranial artery occlusions is the therapeutic goal in stroke therapy [6]. Currently available treatment strategies aimed at restoring blood flow in acute ischemic stroke patients include thrombolytic agents (such as intravenous (IV) or intra-arterial thrombolysis with recombinant tissue plasminogen activator (rtPA)) and/or neurothrombectomy devices for mechanical clot retrieval, followed by rehabilitation through specialized supportive care.

IV lytics have several limitations; one being narrow therapeutic window. They are used in Europe and the United States for patients presenting up to 4.5 hours after symptom onset. Although in the US they are only FDA approved for use in patients presenting up to 3 hours after symptom onset, US national clinical practice guidelines [4, 7] recommend also administering IV lytics in the 3-4.5h window to those patients who meet the ECASS 3 trial inclusion/exclusion criteria [8]. In addition to time constraints, IV thrombolytic therapy has been demonstrated to be less effective in recanalizing proximal large vessel occlusions, such as the ICA and MCA. Since a large percentage of strokes presenting at hospitals are large vessel occlusions, this is an important clinical challenge to address. Additionally, not all patients may be treated with thrombolytic therapy due to contraindications, and so mechanical thrombectomy is a valuable alternative in patients contraindicated to t-PA or where t-PA treatment was not effective.

1.2 State of Art

Endovascular mechanical revascularization (thrombectomy) is an increasingly used method for intracranial large vessel recanalization in acute 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. Since the introduction of stent-retrievers, multiple randomized trials showed the efficacy of endovascular therapy in conjunction with IV-tPA over IV-tPA alone in acute ischemic stroke patients [9, 10, 11, 12, 13, 14, 15, 16, 17]. Other RCTs have provided comparative performance of different thrombectomy devices [18, 19, 20, 21].

The following are lists of relevant RCTs grouped as mechanical thrombectomy vs. IV-tPA or grouped as mechanical thrombectomy device vs. comparator device.

Mech. Thrombectomy vs Medical management or IV-tPA

- MR RESCUE [22]
- IMS III [23]
- Synthesis [24]
- THERAPY [25]
- MR CLEAN [10]
- EXTEND-IA [11]
- REVASCAT [26]
- SWIFT-PRIME [9]
- ESCAPE [27]
- THRACE [14]
- DEFUSE 3 [15]
- PISTE [16]
- DAWN [17]

Device vs. Device

- SWIFT [18]
- TREVO 2 [19]
- ASTER [20]
- 3D Retriever [21]

While the benefit of mechanical thrombectomy in AIS patients with LVO has been demonstrated in comparison to IV-tPA alone, continuing efforts are made to maximize benefit for patients and reduce complications. These investigations generally seek to determine optimal interaction between thrombectomy device and thrombus to improve successful revascularization rates [20, 21, 28, 29]. Most mechanical thrombectomy techniques may be categorized as follows:

- use of stent retrievers by incorporation of the clot through the stent retriever struts after passive stent opening with subsequent withdrawal of the device, with or without flow arrest by a balloon guide catheter [28, 29],
- A Direct Aspiration First-Pass Technique for thrombectomy (ADAPT) with a large bore aspiration catheter placed at the face of the thrombus [20, 29, 30] - This technique utilizes aspiration as the first approach to revascularize the occluded vessel, and if this strategy fails, then the aspiration catheter is used in conjunction with a stent retriever to obtain revascularization.,
- a combination of stent retriever and aspiration catheter, where the stent retriever is usually withdrawn into an intracranially placed aspiration catheter [21, 29].

More significant though, are the most recent RCTs providing evidence refining patient selection to expand the range of patients benefiting from mechanical thrombectomy [14, 15, 16, 17].

The most significant new literature are the results of the DAWN [17] and DEFUSE 3 [15] trials, which demonstrated significant improvement in clinical outcomes for patients treated with mechanical thrombectomy as late as 6 to 24 hours since last seen well.

The DAWN trial used clinical imaging mismatch (a combination of NIHSS score and imaging findings on CTP or DW-MRI) as eligibility criteria to select patients with large anterior circulation vessel occlusion for treatment with mechanical thrombectomy between 6 and 24 hours from last known to be well. Clinical imaging mismatch criteria were defined in three ways: patients ≥80 years old were included if NIHSS ≥ 10 and infarct volume <21 ml; patients <80 years old were included if NIHSS ≥ 10 and infarct volume <31 ml, or if NIHSS ≥20 and infarct volume of 31ml to <51 ml. The trial demonstrated an overall benefit in functional outcome at 90 days in the patients treated with mechanical thrombectomy compared to patients who received only medical management (mRS score 0–2, 49% versus 13%).

The DEFUSE 3 trial used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last known to be well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%). Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not.

1.2.1 Performance

In these studies, the proportion of patients experiencing procedural revascularization success (defined as TICI scores of 2b to 3) ranged from 76% in [15] to 85.4% in [20] when reported after all procedures. For the two studies also reporting revascularization success after a set number of passes, it ranged from 63% in [20] to 81.9% in [21]. Patients achieving functional independence (defined as 90-Day mRS scores of 0-2) ranged from 38% in [25] up to 53% in [14]. While these performance results may not convey the entirety of patient benefit, they provide an approximate quantification of the benefit AIS patients may derive from state of the art treatment with mechanical thrombectomy.

1.2.2 Safety

Assessing the same studies for safety outcomes, mortality rates three months after procedure ranged from 22.7% at the highest [21] to 12% at its lowest [25]. Symptomatic intracerebral haemorrhage (sICH) ranged from 9.3% at the highest [25] to 0% at its lowest [16]. Other reported complications and adverse events included (highest values shown): ICH of any kind: 46% [20]; parenchymal hematoma: 17.4% [20]; neurological deterioration: 14% [17]; embolization in new territory (ENT): 6% [14]; vascular perforation: 2.6% [20]; dissection: 3% [14]; vascular spasm: 23% [14]; new ischemic stroke in different territory: 9.1% [16]; and access site complications: 2% [14].

1.2.3 Unmet needs

Though success rates are high when utilizing mechanical thrombectomy, there are still a proportion of patients for which adequate reperfusion cannot be achieved, certainly, in part, due to the clot not being retrieved. There is a need to study better options for these challenging situations where the current stent retrievers are unsuccessful during the first few attempts at clot removal.

1.3 Study Device

1.3.1 Description

NIMBUS is composed of a self-expanding nitinol cage that engages with a clot upon device deployment. The nitinol cage is connected to the distal end of a tapered (guidewire-like), PTFE coated nitinol shaft, and has radiopaque markers located immediately distal and proximal to the nitinol cage.

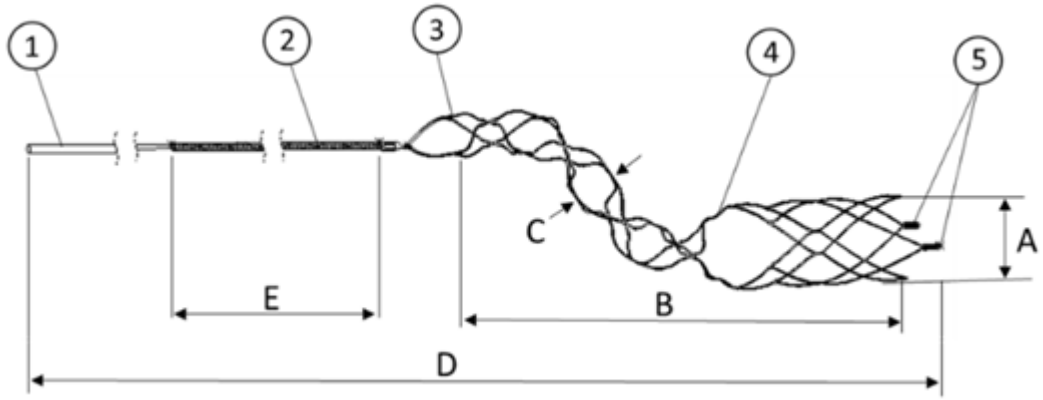
NIMBUS is an innovative design, intended to engage with and retain clots of various type and composition.

The design of NIMBUS is shown in Figure 2, with relevant dimensional information and annotated design features. The laser-cut nitinol cage on the NIMBUS device is shaped into two sections, a proximal or “spiral” section, and a distal or “barrel” section. The proximal section has a gradual spiral shape, rather than a straight cylindrical shape. The distal section of the cage is barrel shaped with a truncated distal end. As the microcatheter is retracted, the wider distal section is unsheathed first and begins to expand. This section is designed to facilitate clot entry and engagement within the struts of the cage during expansion of the device within the clot, similar to other stent-retriever devices. The more proximal section of the Nitinol cage is set in a spiral configuration and has a 2-cell circumferential pattern. This design allows deep engagement of clot in smaller vessels, yet also facilitates clot engagement in larger vessels through the OD created by the entire spiral section. Hence, clot may become engaged within the struts of the spiral structure or in the space created within the spiral formation. The NIMBUS nitinol cage design has demonstrated successful removal of both firm and soft clots through both in vitro and in vivo studies, and the spiral section design, in particular, facilitates removal of fibrin-rich clots which can be challenging in some cases.

The design features of NIMBUS provides physicians with a device offering that is compatible with the various retrieval techniques widely used in mechanical thrombectomy procedures throughout Europe.

NIMBUS is supplied preloaded within an insertion tool – a transparent, PTFE tube incorporating an orange stripe. In use, the physician inserts the insertion tool into the hub of a pre-positioned microcatheter and advances the device through the insertion tool and into the microcatheter. The orange stripe makes the tool easy to identify if needed to reload the device for an additional pass. NIMBUS does not contain any medicinal substances, tissues, or blood products.

Figure 2: Annotated schematic of NIMBUS components



1. Shaft/Push wire; 2. Proximal Radiopaque Coil; 3. Nitinol Cage; 4. Gold Markers (X2); 5. Distal Radiopaque Coils (X2)

Dimensions A to E are specified in the IFU.

1.3.2 Device Storage and Stability

The NIMBUS device should be stored in accordance with the IFU.

1.3.3 Device Acquisition

The CERENOVUS NIMBUS Geometric Clot Extractor (NIMBUS) is CE marked and manufactured by CERENOVUS. The device will be ordered by the sites through standard commercial means. Shipments will not be tracked for this study, devices will be fully traceable though the company's 21 CFR 820 and ISO 13485 complaint quality system.

1.3.4 Device Returns

Any suspected device malfunction with NIMBUS should be properly documented on the Electronic Case Report Forms (eCRFs). In the event of a suspected malfunction, the device shall be returned to CERENOVUS per the address below for analysis. Sites will retain tracking information. All study devices should be returned to:

[redacted]

1.3.5 Indication

The NIMBUS is intended to be used to restore blood flow in patients experiencing an acute ischemic stroke due to a large vessel neurovascular occlusion. The Device is designed for use in the anterior and posterior neurovasculature in vessels of diameter 1.5 mm to 5.0 mm, such as the internal carotid artery, the M1 and M2 segments of the middle cerebral artery, the A1 and A2 segments of the anterior cerebral artery, the basilar, the posterior cerebral and the vertebral arteries.

The Device should only be used by physicians trained in neurointerventional catheterization and the treatment of ischemic stroke.

1.3.6 Endovascular procedure with NIMBUS

The endovascular treatment of stroke is performed per each institution's standard procedure according to the NIMBUS Instructions for Use (IFU), the inclusion/exclusion criteria, and to the procedures as outlined in this study protocol.

1.3.6.1 Preparation & Delivery

Using standard interventional techniques, access the arterial system and using angiography, determine the location of the occluded vessel. Advance an appropriate Guide Catheter, Sheath or Balloon Guide Catheter as close to the occlusion site as possible. Connect a rotating hemostasis valve (RHV) to the proximal end of this catheter and connect to a continuous flush system.

With the aid of a suitable Guidewire, and using standard catheterization techniques and fluoroscopic guidance, an appropriately sized Microcatheter is advanced up to and across the occlusion so that the distal end of the Microcatheter is positioned distal to the occlusion. The guidewire is removed, and NIMBUS is inserted and advanced into the Microcatheter, with the use of the Insertion Tool.

1.3.6.2 Positioning and Deployment

Continue to advance NIMBUS until the radiopaque distal markers approach the distal region of the Microcatheter. NIMBUS should be positioned in the clot ideally such that the end of the proximal radiopaque coil is aligned with the proximal face of the clot (Figure 3). To fully deploy NIMBUS within the clot, retract the Microcatheter until the distal tip of the Microcatheter is positioned over the proximal radiopaque coil of NIMBUS.

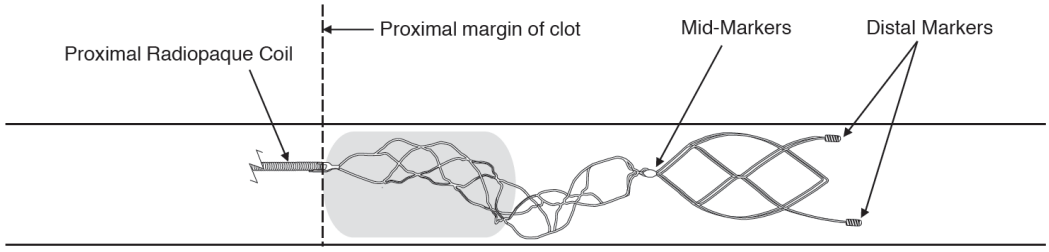


Figure 3: NIMBUS Positioning

1.3.6.3 Retrieval

Prior to clot retrieval re-advance the Microcatheter to the clot while holding NIMBUS push wire static until resistance is met. Do not continue to advance against significant resistance. Withdraw NIMBUS and Microcatheter slowly and carefully as a single unit to the Guide Catheter while aspirating through the guide, and maintaining Microcatheter and NIMBUS position relative to each other during the withdrawal step. Applying vigorous aspiration (by syringe), withdraw NIMBUS and Microcatheter into the Guide Catheter and continue to aspirate until NIMBUS reaches the RHV on the guide. Disconnect the RHV from the guide and remove NIMBUS, Microcatheter and RHV together from the guide.

1.3.6.4 Cleaning and Re-use

NIMBUS may be used for up to three retrieval attempts. If an additional pass is to be made with NIMBUS, then carefully remove any captured thrombus from NIMBUS, and clean NIMBUS in heparinized saline, rubbing gently from proximal to distal to remove any residual thrombus material. Then, follow the same preparation, delivery, and retrievals steps, as described in the NIMBUS IFU. Do not attempt more than three retrieval attempts in one vessel.

1.4 Potential Risks and Benefits

The risks and benefits of participating in the study will be explained in the voluntary written informed consent that must be obtained from all subjects.

1.4.1 Contraindications

- Allergy or hypersensitivity to Nickel-Titanium.
- Excessive vessel tortuosity that may prevent device delivery.
- Patients with angiographic evidence of carotid dissection.

1.4.2 Potential Complications

Risks that may be associated with the use of NIMBUS can be found in the commercially available IFUs found with the device.

1.4.3 Potential Benefits from use of NIMBUS

Although there may be no direct benefits of study participation, subject participants records will undergo an enhanced level of clinical scrutiny compared to routine SOC, which may provide some indirect health benefits. The potential benefits of this commercially approved device outweigh any anticipated risks.

2 OBJECTIVES AND PURPOSE

The objective of this study is to assess the efficacy of NIMBUS in a real-world setting in patients where the first one or two passes with another Mechanical Thrombectomy therapy have not achieved mTICI 2b or better.

The rate of effectiveness achieved will be considered as we design further studies. The study will also report on clot characteristics and clinical outcomes.

3 STUDY DESIGN, ENDPOINTS, AND OTHER ANALYSES

3.1 Description of the Study Design

This is a prospective, multi-center, single-arm, observational post market study that will consecutively enroll up to 50 subjects treated with NIMBUS at approximately 10 sites in Europe. This study will evaluate NIMBUS, post one or two unsuccessful passes of another Mechanical Thrombectomy device, in the treatment of acute ischemic stroke. Data will be collected at baseline (prior to thrombectomy), during the procedure, and post-procedure. Clinical follow up with subjects will occur over 3 months; at 24 hours, and 90 days post procedure.

3.2 Study Endpoints

3.2.1 Primary Endpoint

1. **Successful Revascularization (mTICI ≥ 2b) with NIMBUS as determined by an Independent Core Lab.**

   The primary endpoint is successful revascularization after the final pass of NIMBUS, as determined by an Independent Core Lab, where the successful revascularization is defined as achieving an mTICI score of 2b or greater. In this study, revascularization will be measured by an independent adjudicating Imaging Core Lab and reported using the Expanded Thrombolysis in Cerebrovascular Infarction (eTICI), inclusive of the 2C rating (Table 2). For purposes of data comparisons, a minimum threshold of mTICI 2b is equal to eTICI 2b50.

Table 2: eTICI inclusive of the 2c rating

eTICI (inclusive of the 2C rating) scale [31, 32, 33, 34, 35]	
0	No reperfusion; 0% filling of the downstream territory.
1	Thrombus reduction without any reperfusion of distal arteries.
2	2a Reperfusion in less than half (1-49%) of the territory. 2b50 Reperfusion in (50-66%) of downstream territory. 2b67 Reperfusion in (67-89%) of downstream territory. 2c Reperfusion in (90-99%) of downstream territory.
3	Complete or 100% reperfusion.

3.2.2 Secondary Endpoints

The secondary endpoints are pre-specified below and have been identified as outcomes meaningful to evaluate the effectiveness and safety of stroke treatment with NIMBUS.

1. **Successful Procedural Revascularization (final mTICI ≥ 2b)**

   Rate of achieving an mTICI score of 2b or greater (Table 2) at the end of the procedure, as determined by an Independent Core Lab.

2. **Excellent Procedural Revascularization (final mTICI ≥ 2c)**

   Rate of achieving an mTICI score of 2c or greater (Table 2) at the end of the procedure, as determined by an Independent Core Lab.

3. **First Pass Revascularization using Nimbus (mTICI ≥ 2b)**

   Rate of achieving an mTICI score of 2b or greater(Table 2) after the first use of NIMBUS (whether on the second or third pass), as determined by an Independent Core Lab.

4. **Occurrence of Embolization to a New Territory (ENT)**

   Rate of embolization in a previously unaffected territory, following the final pass of NIMBUS.

5. **Symptomatic Intracerebral Hemorrhage (sICH) at 24 hours specified according to the Heidelberg Bleeding Classification (HBC)**

   Rate of sICH at 24 hours post-procedure. Symptomatic Intracerebral Hemorrhage (sICH) is defined per the Heidelberg Bleeding Classification (Table 3).

Table 3: Definition of Symptomatic Intracerebral Hemorrhage

Heidelberg Bleeding Classification (HBC) [36]
SICH: new intracranial hemorrhage detected by brain imaging associated with any of the item below: • ≥4 points total NIHSS at the time of diagnosis compared to immediately before worsening. Note that a 4 points change is not compared with the baseline admission NIHSS score but instead to the immediate predeterioration neurological status. • ≥2 point in one NIHSS category. The rationale for this is to capture new hemorrhages that produce new neurological symptoms, making them clearly symptomatic but not causing worsening in the original stroke territory. For example, a new remote hemorrhage in the contralateral occipital lobe may cause new hemianopia that is clearly symptomatic but the patient will not have worsening of ≥4 points on the NIHSS score. • Leading to intubation/hemicraniectomy/EVD placement or other major medical/surgical intervention. • Absence of alternative explanation for deterioration.

6. **90 Day All-Cause Mortality**

   Rate of all-cause mortality at 90 days post-procedure.

7. **Modified Rankin Scale (mRS) of ≤ 2 at 90 days**

   Rate of independence (mRS of ≤2) at 90 days post-procedure.

3.3 Ancillary Endpoints

3.3.1 Clot Analysis

Histopathologic analysis of Clot Collected – Composition of clot components, per pass, to be evaluated including: Red Blood Cells (RBC), White Blood Cells (WBC), platelets, fibrin and other proteins, as evaluated by the independent Central Lab.

3.3.2 Hospitalization Analysis

Medical Resource Utilization and Health Economics related data including:

1. Hospitalization length of stay for index procedure and unscheduled re-hospitalizations.
2. Healthcare resource utilization for index procedure, post-procedure and re-hospitalizations for unscheduled events.

4 STUDY POPULATION

Prior to inclusion in the study all subjects will be screened for study eligibility. Therefore, clinical site personnel will review the subject's medical history.

4.1 Inclusion Criteria

Prior to entry in this study, patients must meet **ALL** of the following criteria:

1. Age ≥ 18.
2. The subject or the subject's legally authorized representative has signed and dated an Informed Consent Form.
3. Patient has had one or two passes of another mechanical thrombectomy device without achieving mTICI 2b or better and continues to have angiographic confirmation of a Large Vessel Occlusion (LVO) in the same vessel.
4. mRS 0-1 prior to this stroke.
5. NIMBUS is used on the second or third overall pass to attempt revascularization.

4.2 Exclusion Criteria

Patients must be excluded from this study if **ANY** of the following criteria are met:

1. Currently participating in an investigational (drug, device, etc.) clinical trial that may confound study endpoints. Patients in observational, natural history, and/or epidemiological studies not involving intervention are eligible.
2. Confirmation of positive pregnancy test according to site specific standard of care (e.g. test, verbal communication).
3. All patients with severe hypertension on presentation (SBP > 220 mmHg and/or DBP > 120 mm Hg). All patients, in whom intravenous therapy with blood pressure medications is indicated, with hypertension that remains severe and sustained despite intravenous antihypertensive therapy (SBP >185 mmHg and/ or DBP >110 mmHg).
4. Known cerebral vasculitis.
5. Known cancer with life expectancy less than 12 months.
6. Stenosis, or any occlusion, in a proximal vessel that requires treatment or prevents access to the site of occlusion.
7. Intracranial stenosis that prevents access to the site of occlusion.
8. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) evidence of recent/ fresh hemorrhage on presentation.
9. Baseline computed tomography (CT) or MRI showing mass effect or intracranial tumor (except small meningioma).
10. Evidence of dissection in the extra or intracranial cerebral arteries.
11. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation).

4.3 Study Duration

The duration of the study is expected to be approximately 33 months. This includes an enrolment period of approximately 30 months and a post-treatment follow-up evaluation of 3 months.

4.4 Number of Subjects

Up to 50 subjects will be consecutively enrolled into the study which will involve treatment with the NIMBUS device.

A minimum of 3 subjects will be enrolled per site, to ensure generalizability of results and to minimize the influence of any single site, no more than approximately 25% of the total enrollment will be allowed at a single site (i.e., a maximum of 12 subjects enrolled per site).

4.5 Number of Sites

The study will be conducted at approximately 10 institutions in Europe where NIMBUS is approved for commercial use.

4.6 Participant Withdrawal or Termination

4.6.1 Reasons for Withdrawal or Termination

Subjects are free to withdraw from participation in the study at any time upon request. The investigator may terminate participation in the study if any adverse event or other medical condition or situation occurs such that continued participation would not be in the best interest of the participant.

4.6.2 Handling of Participant Withdrawals or Termination

Subjects that withdraw consent after treatment are not required to undergo follow-up after withdrawal. They will not be replaced and will be considered part of the subject cohort. The reason for early withdrawal will be documented in the source documents and case report forms.

In the event a subject withdraws from the study, their data will be excluded from the data analysis from the time of withdrawal going forward. All data collected prior to withdrawal will be included in for data analysis, as permitted per country regulations.

5 STUDY PROCEDURES AND EVALUATIONS

5.1 Study Specific Procedures

All procedures are expected to follow the standard of care of the sites participating in this study.

5.2 Standard of Care Procedures

The procedures completed as part of this study are standard practice and include collection of relevant medical history, relevant medication history, neurological examination, NIHSS, mRS, imaging (e.g., CT and/or MRI), and review of any AEs. This may vary from site to site.

5.3 Independent Core Laboratory for Image Evaluation

All imaging collected will be SOC, no additional imaging will be requested for this study. Imaging should include full A-P lateral images for the start and the end of each procedural pass. An independent radiographic core laboratory shall be utilized to provide an unbiased and standardized assessment of all collected imaging. All subject protected health information will be removed before an image is uploaded and evaluated. The core lab assessor will be blinded to subjects' previous medical history. Each angiogram will be read independently by experienced Imaging Core Lab neuro-interventionalists.

The objective of the Imaging Core Lab will be to:

- Review all angiograms obtained
- Provide an unbiased assessment of the rate of revascularization defined by mTICI scores based on angiographic imaging from the study sites
- Evaluate CT/MRI examinations to detect and assess hemorrhages.

This study will be collecting the following imaging data to be assessed by Imaging Core Lab:

- Baseline - CT/ MR imaging
    - Infarct volume
    - Clot location
    - Clot length
    - Clot radiodensity on CT / Susceptibility Vessel Sign (SVS) on MRI
- Procedural Angiography
    - mTICI score for every pass
    - Clot location for every pass (proximal face of clot)
    - Emboli to new territories
- Post Procedure - CT/ MR imaging
    - Intracranial Hemorrhage

Hemorrhages will be classified according to the following categories [36]:

- HI 1 – Scattered small petechiae, no mass effect
- HI 2 – Confluent petechiae, no mass effect
- PH1 – Hematoma within infarcted tissue, occupying <30%, no substantive mass effect
- PH2 – Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
- RIH – Parenchymal hematoma remote from infarcted brain tissue
- IVH – Intraventricular Hemorrhage
- SAH – Subarachnoid Hemorrhage
- SDH – Sub Dural Hemorrhage

5.3.1 Imaging Shipment

De-identified images may be sent via DICOM format on a CD (that contains the subject ID, study visit, Sponsor name, and protocol number), or electronically to the core lab website, if available.

5.4 Clot Collection and Processing

Normally, following mechanical thrombectomy, the retrieved clot is discarded. However, for subjects in this study, clot will be collected for follow on analysis. Sites will place the clot collected per pass in a container of neutral buffered formalin solution for preservation. If more than one clot fragment is retrieved during different retrieval attempts / passes, the fragments will be collected per pass into separate containers. Each container will have a unique subject identifier noting the retrieval attempt / pass number on the label. This unique identifier will be entered in the eCRF by the site along with other relevant data and linked to the subject ID. Samples will subsequently be shipped by the site to the independent Central Lab for follow on analysis (Section 5.4.1).

All materials for collecting, processing and shipping samples to the independent Central Lab will be provided by the Sponsor or the Sponsor's selected vendor. For additional details on sample processing refer to Clot Collection and Processing Manual provided by CERENOVUS.

5.4.1 Independent Central Lab for Clot Evaluation

Clot materials collected for this study will be processed by the independent Central Lab. Standardized procedures and techniques have been established by the independent Central Lab for the analysis of AIS clots. These techniques comprise of morphological and histological testing, which will help in defining clot features and clot compositional analysis for this study.

Samples will be stored until the research and development testing is completed or the sample is completely used. Leftover specimens not used in the immediate research will be stored for future use in research that will aid in understanding the etiology of the disease.

5.5 Neurological Evaluations

The following neurological evaluations will be used in this study and are part of SOC:

NIHSS Score - The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a subject's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

The modified Rankin Scale (mRS) - The mRS is a scale commonly used to measure the degree of disability or dependence in the daily activities in subjects following stroke or other neurologic event and is conducted by a qualified evaluator. It is a scale with seven categories ranging from no symptoms to severe disability and death. Qualifications of evaluator training will be documented for this study. The 90 day mRS must be performed by a qualified independent evaluator who is not part of the interventional treating team.

6 STUDY SCHEDULE

Study subjects will be managed by the respective Investigators and his/her staff according to the current standard procedures at each participating study site. Data will be collected according to the defined schedule listed in Table 1.

6.1 Screening

Subjects presenting with AIS to the enrolling medical treatment facility will be evaluated and treated by the physician according to the institutional practice prior to enrolment in the study. A subject can be consented to participate in this study from the point of imaging confirming a large vessel occlusion up to 7 days post-procedure. Subjects will be screened against the study inclusion/exclusion criteria to determine their initial eligibility. The final eligibility criterion is the requirement for a second pass of a mechanical thrombectomy device during the index procedure, therefore, the screening log should be completed post procedurally for all AIS patients in whom a second mechanical thrombectomy pass was completed. All subjects screened will be documented on the Screening/Enrolment log, including the reason for non-participation for subjects who do not enroll.

All assessments and imaging performed for this study are part of SOC for stroke treatment. Informed consent is mandatory and must be obtained before any data is captured in the eCRF.

During the eligibility screening, the investigator will perform an initial evaluation of potential study subjects for study eligibility according to inclusion / exclusion criteria. For subjects who meet the eligibility criteria and agree to participate, informed consent will be obtained. The investigator, or designee, will explain the research study to the subject and/or the legally authorized representative and answer any questions that may arise. The possible risks and possible benefits of participation will be discussed. The subject and/or the legally authorized representative will be asked to read, review and sign the EC approved informed consent form. The informed consent process is detailed further in Section 10.3.

A subject is considered enrolled in this study after the physician confirms the subject meets all eligibility criteria, and the subject is consented.

All subjects *who provide written informed consent* will be entered into eCRF regardless of whether or not they participate in the study.

6.2 Baseline Assessments

The following information is assessed or collected as part of the standard of care and will be collected in the eCRF and maintained as source records at the study site:

- Demographics (including ethnicity & race).
- Relevant medical history.
- Verification of inclusion/exclusion criteria.
- Patient functional status prior to the study stroke event will be evaluated using modified Rankin Scale (mRS) for all subjects.
- Neurological status will be evaluated using the NIHSS score for all subjects.
- Relevant medication history will be collected from a subject interview and a review of the subject's medical records if necessary. Specifically, t-PA delivered prior to and during the procedure will be the only medication collected.
- Computed tomography (CT) or magnetic resonance imaging (MRI) obtained prior to study enrolment will be used for baseline assessment.

6.3 Procedure Assessments

Immediately prior to introducing a guide catheter, the physician will perform an angiogram of the affected intracranial artery. The angiogram will be done using standard techniques (subtracted complete runs from arterial to venous phase initially and at end of procedure). The purpose of the pre-procedure angiogram is to confirm:

- the location of the occlusion;
- that the subject remains suitable for treatment with mechanical thrombectomy;
- that the subject remains a candidate for the study per the eligibility criteria.

In the event that the subject is excluded as a result of the angiogram, the subject will be considered a screen-failure and will not require any study follow-up.

Subjects will have challenging occlusions, with mTICI ≤ 2a post one, or two passes, of another Mechanical Thrombectomy device. Any commercially available Mechanical thrombectomy device (i.e. either aspiration or Stent-retriever other than NIMBUS) may be used during the first and up to two vessel clearance attempts. The physician may use his own discretion on whether to introduce the NIMBUS after one failed vessel clearance attempt, or after two. The NIMBUS must be used no later than the overall third procedural pass for the patient to be eligible. Up to 50 subjects will be treated with the NIMBUS.

Once the decision has been made to use NIMBUS, it is used for up to three passes. After the third pass with the NIMBUS, if the physician would like to utilize another device/technique for treatment, they may. Angiographic imaging will be collected per every pass for subsequent review by an independent Imaging Core Lab. Clot will also be collected per every pass for analysis in an independent Central Lab.

Endovascular treatment with NIMBUS, and the other stent-retrievers, is performed per hospital standard technique and in accordance with the applicable devices' IFU.

The following data will be captured during the procedure, and recorded on the eCRF:

- Name of the treating physician.
- Type of sedation used.
- Vessel location of the occlusion being treated per pass.
- mTICI scores per pass (Pre-device deployment and post-device retrieval).
- Names and sizes of stent-retrievers used per pass.
- Lot number of NIMBUS used, as applicable.
- Ancillary devices used (e.g., balloon guides, microcatheters) per pass.
- Details of the technique used per pass.
- Relevant time points during the procedure (e.g. arterial puncture time).
- Clot collection for every pass during the procedure.
- Additional interventions performed (if applicable)

In addition, the following will be collected throughout the procedure and recorded on the eCRF.

- AEs
- Protocol deviations
- Device malfunctions/deficiency

The procedural angiogram will be provided to the Independent Core Lab.

6.3.1 Rescue therapy

Rescue therapy is not applicable for this study.

6.4 24 hours (±8 hours) Post-Procedure Assessment

Following the procedure, subjects will be assessed at 24 hours (±8 hours) post-procedure. The following information will be collected in the eCRF and the documentation will be maintained as source records at the study site:

- NIHSS assessment
- CT or MR imaging
- Relevant AEs

6.5 90 Days (±14 Days) Follow-up Assessment

A 90-Day follow-up assessment may be conducted for all subjects during an office visit or a telephone interview. The following information will be collected in the eCRF and the documentation will be maintained as source records at the study site:

- mRS assessment (must be performed by a qualified independent evaluator who is not part of the interventional treating team, and if assessment is done via telephone, it should be noted in source documents)
- NIHSS assessment (optional)
- Relevant AEs

6.6 Unscheduled Follow-up Visit

Assessments should be completed for unscheduled visits from the time of Discharge up to (but not including) the 90-day Follow-up, where imaging, NIHSS, or mRS is performed as part of stroke management care for the subject. Corresponding data must be documented on the eCRF and submitted to the Sponsor.

6.7 Early Termination

During the course of the study, it is possible that subjects will discontinue the study. Factors leading to subject early termination may include, but are not limited to the following:

- Subject withdraws consent prior to completion of all study follow up requirements.
- The Investigator decides to discontinue subject's or site's participation in the study (e.g. if the investigator has a concern about the study conduct or device).
- The subject is lost to follow-up.
- Death (Provided the consent is still in place, the subject's records will be included).
- The study is terminated at a site or as a whole.

The study can be discontinued at the discretion of the investigator or study Sponsor for reasons including, but not limited to, the following:

- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary

- Insufficient recruitment of subjects
- Persistent non-compliance of a site with the protocol, or EC regulatory requirements

If the study is discontinued or suspended prematurely at a single clinical site (e.g. due to non-compliance or lack of enrollment), the Sponsor shall inform the clinical investigator/investigational center of the termination or suspension in enrollment and the reason for this. The Sponsor will also inform site personnel that although enrollment will be halted, the currently enrolled subjects will continue to be followed per protocol through the 90-day follow-up visit and then be exited from the study. The Sponsor's communication to the investigator/investigational center will also include instructions for the investigator to promptly inform the EC regarding the change in study status, along with the reason for termination or suspension by the Sponsor.

If the entire study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigators/investigational centers of the termination or suspension in enrollment and the reason for this.

6.8 Lost to Follow-Up

If, despite the following measures, a subject does not return for a scheduled study visit, site personnel should immediately contact the subject to reschedule the visit. All attempts made by the Study Site staff to contact the subject should be documented in the subject's medical record or office chart. A subject will not be considered lost to follow-up until their final study visit.

To prevent and/or reduce loss to follow-up the following measures will be implemented for this study:

- The Informed Consent will provide a clear explanation of the expected duration of the subject's participation in the study and a description of the study follow-up requirements to ensure subjects understand and agree to the study requirements.
- At the time each subject is enrolled in the study, sites will obtain contact information for the subject.
- Site personnel will be encouraged to question the subject about any difficulties with adhering to the study schedule. If underlying conditions are identified, the site will make reasonable efforts to address these conditions on a case by case basis, and this may require site arrangements or schedule adjustments to allow the subject to continue study participation.
- For each missed or overdue follow-up visit, site personnel will document the reason for the missed or overdue follow-up visit in the subject's medical record or office chart.
- Site personnel re-training will be conducted by CERENOVUS or their representatives remotely, when needed, to reinforce the follow-up visit requirements and the necessity of adhering to the protocol's follow-up schedule.

6.9 Schematic of Study Design

A subject can be consented in the study from the point of arrival at the treating site up to 7 days post-procedure. Assessments and imaging performed for the study are part of standard of care (SOC) for stroke treatment, and screening can occur without obtaining consent. Informed consent is mandatory and must be obtained before any data is captured in the electronic Case Report Form (eCRF). Figure 1 shows a schematic of the study design.

6.10 Schedule of Assessments Table

The schedule of all follow-up visits including imaging procedures as well as the data to be collected at each visit is shown in Table 1.

7 SAFETY ASSESSMENT

7.1 Specific Safety Parameters

For purposes of obtaining long-term safety surveillance in this study, **AEs will be reported and recorded (via eCRF) if any of the following apply:**

- The event is neurological in nature
- The event is a serious adverse event (SAE)
- Causality is related to:
  - The device, or
  - The procedure, or
  - If causality is unknown

7.1.1 Adverse Event (AE)

An **Adverse Event (AE)** is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device (ISO 14155).

- **Note 1:** This definition includes events related to the investigational medical device or the comparator.
- **Note 2:** This definition includes events related to the procedures involved.
- **Note 3:** For users or other persons, this definition is restricted to events related to the investigational medical devices

Any medical condition that is present at the time the participant is screened or prior to the start of the study procedure will be considered as baseline and not reported as an AE. Such conditions should be added to medical history, if not previously reported.

7.1.2 Serious Adverse Event (SAE)

A **Serious Adverse Event (SAE)** is defined (ISO 14155) as an AE that:

a) led to a death,

b) led to a serious deterioration in the health of the subject that either resulted in:
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, or
   3) in-patient hospitalization or prolonged hospitalization, or
   4) medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

- **Note:** A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a SAE.

7.1.3 Adverse Device Effect (ADE)

An **Adverse Device Effect (ADE)** is defined as an AE related to the use of an investigational medical device (ISO 14155).

- **Note 1:** This definition includes AEs resulting from insufficient or inadequate IFU, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- **Note 2:** This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

7.1.4 Serious Adverse Device Effect (SADE)

A **Serious Adverse Device Effect (SADE)** is an ADE that has resulted in any of the consequences characteristic of an SAE (ISO 14155).

7.1.5 Unanticipated Serious Adverse Device Effect (USADE)

An **Unanticipated Serious Adverse Device Effect (USADE)** is a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (ISO 14155).

- **Note:** Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

7.1.6 Device Deficiency, Device Malfunction, and Use Error

All study device deficiencies shall be documented in the eCRF throughout the clinical investigation and appropriately managed by the Sponsor. If a study device deficiency is detected or suspected that could have led to an SADE, it should be documented on the appropriate eCRF, and the device failure and AE (if applicable) must be reported to the Sponsor within 72 hours upon study site staff awareness. All non-study device malfunctions should be reported via the manufacturer's complaints handling process.

- A **device deficiency** is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.
  - **Note:** Device deficiencies include malfunctions, use errors, and inadequate labeling.
- **Device malfunction** is defined as a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU or clinical investigation plan.
- **Use error** is defined as the act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.
  - **Note 1:** Use error includes slips, lapses, and mistakes.
  - **Note 2:** An unexpected physiological response of the subject does not in itself constitute a use error (ISO 14155).

7.2 Adverse Event Severity, Causal Relationship Ratings and Expectedness

The Investigator will record the nature, severity, treatment and outcome of the AE, and will determine the relationship to device and procedure and in the case of SADEs whether the event was anticipated or not.

This classification of the event determines the reporting procedures to be followed. The Medical Monitor (MM) may upgrade the classification as required for reporting purposes.

For purposes of this protocol, the following definitions will apply:

- Adverse Event Severity
- Causal Relationship Rating
- Outcome

7.2.1 Adverse Event Severity

The intensity or severity of each AE must be assessed according to the following classifications:

Table 4: Adverse Event Severity Definitions

Mild	Awareness of signs, symptoms, or events that are otherwise easily tolerated that may result in minimal transient impairment of a body function or damage to a body structure, but do not require intervention other than monitoring.
Moderate	Any event that results in moderate transient impairment of a body function or damage to a body structure that causes interference with usual activities, or that warrants possible intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
Severe	Any event that is incapacitating (an inability to do usual activities) or is life-threatening and results in permanent impairment of a body function or damage to a body structure, or requires intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

7.2.2 Causal Relationship Rating

The clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Table 5: Adverse Event Causality Classifications

Caused By	Relation	Definition of Relation
Device	Causal relationship	The event is associated with the investigational device beyond reasonable doubt
	Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained
	Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely
	Unlikely	The relationship with the use of the investigational device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained
	Not related	Relationship to the investigational device can be excluded

Caused By	Relation	Definition of Relation
Study Procedure	Causal relationship	The event is associated with the study procedure beyond reasonable doubt
	Probable	The relationship with the study procedure seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained
	Possible	The relationship with the study procedure is weak but cannot be ruled out completely
	Unlikely	The relationship with the study procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained
	Not related	Relationship to the procedure can be excluded

7.2.3 Outcome

The outcome of each AE must be assessed according to the following classifications:

Table 6: Adverse Event Outcome Classifications

Classification	Definition
Recovered/Resolved	Subject fully recovered with no observable residual effects
Recovered/Resolved with sequelae	Subject recovered with observable residual effects
Recovering/Resolving	Subject's condition improving, but residual effects remain
Not Recovered/Not Resolved	AE is ongoing without improvement in the overall condition
Fatal	Subject died as a result of the AE (whether or not the AE is related to the device or procedure)
Unknown	AE outcome is unknown (e.g., subject is lost to follow-up)

7.3 Time Period and Frequency for Adverse Event Assessment and Follow-up

AEs shall be assessed and documented for all enrolled eligible subjects from the start of the procedure or time of consent, whichever is earlier, to the end of the study participation or until their withdrawal, whichever occurs first. AEs will not be collected by the Sponsor until after consent is obtained from the subject and/or the legally authorized representative. AEs that occur during this study should be treated by established standards of care which will protect the life and safety of the subject. Events will be followed for outcome information until resolution, stabilization or the subject exits the study, whichever occurs first. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events.

7.4 Recording Adverse Events

The study site personnel must seek information on AEs by specific questioning and, as appropriate, by examination. Information on each AE should be recorded immediately in relevant source documents, and also on the appropriate eCRF. The following attributes must be assigned by the Investigator:

- Description of the event
- Dates of onset and resolution
- Determination if event is serious
- Determination if the event is anticipated – in the event of an SADE
- Determination of event severity
- Determination of the causal relationship to study device and study procedure.

The clinical course of each event will be followed until resolution or stabilization or the subject exits the study, whichever comes first.

7.5 Reporting Procedures

7.5.1 Adverse Event Reporting Requirements

The reporting requirements from site to sponsor are summarized in Table 7.

Table 7: Adverse Event Reporting Requirements

Type of Adverse Event	Reporting Requirements
• SAE • SADE • USADE • Death • Any study device deficiency that could have led to an SADE*	Report to Sponsor immediately upon study site staff awareness of event but no later than 72 hours.
• All other AEs • All other study device deficiencies*	Report to Sponsor immediately upon study site staff awareness, but no later than 14 calendar days.

* Non-study device deficiencies should be reported via the manufacturer's complaints handling process.

- In the event electronic data capture (EDC) is unavailable, AEs can be notified via email to the SPERO study mailbox: [redacted].
  Note: the AEs will still need to be recorded on eCRFs once EDC is functional.

NIMBUS deficiencies should not be reported as AEs unless an AE results from this deficiency.

It is the responsibility of the Investigator to comply with 1) his/her EC's requirements for reporting safety events, and 2) any country specific regulatory/CA Investigator reporting requirements for safety events.

7.6 Sponsor Review of AEs

A licensed medical doctor employed by the Sponsor will review all reported adverse events on an ongoing basis. The site reported event term will be reviewed to assess if the event should remain as reported or be re-classified using a term based on the applicable event definition. Recorded AEs will be evaluated by the Sponsor for significance and relevance with respect to trends that may represent a previously unknown or unanticipated risk that may relate to the study device or treatment.

7.7 Device Complaints, Failures, Deficiencies, and Malfunctions

All device complaints, failures, deficiencies (with or without an associated AE), and technical complications must be reported to CERENOVUS Complaint department within **72 hours** of investigator's/Site's knowledge of the event. This device must remain at the site until Sponsor provides instructions on how to return the device for analysis (refer to Section 1.3.4). Another, new device may be used.

8 CLINICAL MONITORING

The study will be conducted in accordance with specific provisions of the associated ECs, the current applicable version of ISO 14155, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP, and the applicable national and regional regulatory requirements.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that study data are accurate, complete, and verifiable, and that study conduct is in compliance with currently approved protocol. Each site will be visited regularly, and subject medical records shall be made available during the visits.

Monitoring visits may include, but are not limited to the following:

- Protocol adherence.
- Source documentation verification and accuracy of the eCRFs as specified in the monitoring plan.
- Verification that informed consent are being obtained for all applicable subjects participating in the study in accordance with requirements described in the study protocol.
- Verification of completeness of the Regulatory Binder.
- Verification of accuracy of all study logs such as the Delegation of Responsibility Log, etc.
- Compliance with applicable regulations.
- Identification and action to resolve any issues or problems with the study.

Data are to be submitted promptly via eCRF after collection. Missing or unclear data will be queried to be corrected as necessary throughout the study. CERENOVUS will request further documentation such as physician notes, outside hospital records, etc. when further documentation is required to understand any AEs. Monitoring will be conducted in accordance with the monitoring plan.

9 STATISTICAL METHODOLOGY

This section describes the statistical methods for the study design and planned analyses of study data. A separate Statistical Analysis Plan (SAP) which provides greater detail on the analyses to be conducted will be developed prior to the planned analyses. Any deviations from the final SAP will be noted in the final clinical report.

9.1 Primary Endpoint

The primary endpoint is successful revascularization after the final pass of NIMBUS, as determined by an Independent Core Lab, where the successful revascularization is defined as achieving an mTICI score of 2b or greater.

9.2 Secondary Endpoints

Secondary endpoints are listed below; further details about these endpoints are provided above in Section 3.2.2 of this protocol. There are no prospectively stated hypotheses associated with these secondary endpoints.

1) Successful Procedural Revascularization (final mTICI ≥ 2b).
2) Excellent Procedural Revascularization (final mTICI ≥ 2c).
3) First Pass Revascularization using NIMBUS (mTICI ≥ 2b).
4) Occurrence of Embolization to a New Territory (ENT).
5) Symptomatic Intracerebral Hemorrhage (sICH) at 24 hours specified according to the Heidelberg Bleeding Classification (HBC).
6) 90 Day All-Cause Mortality.
7) Modified Rankin Scale (mRS) of ≤ 2 at 90 days.

9.3 Ancillary Endpoints

Other analyses are listed below; further detail about these analyses is provided above in Section 3.3 of this protocol. There are no prospectively stated hypotheses associated with these analyses.

1) Clot Analysis
   - Histopathologic analysis of clots collected
2) Hospitalization Analysis

   Medical Resource Utilization and Health Economics related data including:
   - Hospitalization length of stay for index procedure and unscheduled re-hospitalizations.
   - Healthcare resource utilization for index procedure, post-procedure and re-hospitalizations for unscheduled events.

9.4 Levels of Significance

No formal tests of hypothesis are planned. Unless otherwise stated, all confidence intervals will be two-sided 95%.

9.5 Analysis Sets

The following analysis sets are defined in the study:

Modified Intent-to-Treat (mITT) Analysis Set:

The mITT Analysis Set consists of all subjects who are enrolled into the study, and who have attempted at least one pass with the NIMBUS device (which includes deployment and retrieval with the NIMBUS device).

mRS Analysis Set:

In order to define a population more comparable to prior published literature reporting mRS outcomes at 90 days, the mRS Analysis Set has been defined. The mRS Analysis Set consists of all mITT subjects who meet all of the following criteria at baseline:

- MRI criterion: volume of diffusion restriction visually assessed ≤50 mL.
  OR
  CT criterion: ASPECTS 6 to 10 on baseline CT.
  OR
  CTA-source images, or, volume of significantly lowered CBV ≤50 mL.
- NIHSS ≥ 8 and < 30
- Subjects treated within 6 hours of onset of stroke symptoms (start of treatment defined as groin puncture)

9.6 Sample Size Justification

There is no hypothesis testing for this post-market study, approximately 50 treated subjects are deemed sufficient to evaluate the performance of NIMBUS.

Approximately 50 subjects will be consecutively enrolled using commercially available Mechanical Thrombectomy devices during the preceding one or two passes. With an enrolled sample size of up to 50

and an attrition rate of no more than 10%, the precision (margin of error) for the primary endpoint is anticipated to be around 10.1% based on 2-sided 95% confidence intervals, where the primary endpoint rate is estimated to be 86%.

$$Margin\ of\ error \approx 1.96 \times SE$$

$$= 1.96 \times \sqrt{\frac{p(1-p)}{n}} = 1.96 \times \sqrt{\frac{0.86 \times (1-0.86)}{45}} = 10.1\%$$

where SE denotes the standard error and p denotes the proportion of subjects who achieve the primary endpoint.

9.7 Analyses to be Conducted

9.7.1 General Conventions

Descriptive summary statistics will be presented for all endpoints. The number and percentage of subjects will be summarized for categorical variables. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, minimum and maximum.

9.7.2 Disposition of Study Subjects

The number and percentage of subjects in the mITT Analysis Set, together with a summary of subjects who were excluded (i.e. ineligible consented subjects), completed or discontinued the study with associated reasons, will be summarized for all consented subjects.

Enrollment by site will be summarized for all enrolled subjects.

9.7.3 Demographic and Baseline Characteristics

All demographic characteristics, procedural, and immediate post-operative data will be summarized using the mITT Analysis Set.

9.7.4 Primary and Secondary Endpoint Analyses

There are no prospectively stated hypotheses associated with primary or secondary endpoints.

All analyses will be summarized using the mITT Analysis Set unless otherwise defined.

9.7.4.1 Primary Endpoint Analysis

1. **Successful Revascularization (mTICI ≥ 2b) with NIMBUS as determined by an Independent Core Lab.**

   The endpoint is defined as the number and percentage of subjects who have achieved mTICI score of 2b or greater after the final pass of NIMBUS. Two-sided exact 95% confidence intervals will be conducted around the percentage.

   Subjects with missing data on mTICI will be excluded from the analysis.

   The mTICI score will be based on the assessment from the Independent Core Laboratory.

9.7.4.2 Secondary Endpoint Analyses

1. **Successful Procedural Revascularization (final mTICI ≥ 2b)**

   This endpoint is defined as the number and percentage of subjects who have achieved the mTICI score of 2b or greater following the final pass of the procedure.

   The mTICI score will be based on the assessment from the Independent Core Laboratory from the end of the procedure.

2. **Excellent Procedural Revascularization (final mTICI ≥ 2c)**

   This endpoint is defined as the number and percentage of subjects who have achieved the mTICI score of 2c or greater following the final pass of the procedure.

   The mTICI score will be based on the assessment from the Independent Core Laboratory from the end of the procedure.

3. **First Pass Revascularization using NIMBUS (mTICI ≥ 2b)**

   This endpoint is defined as the number and percentage of subjects who have achieved the mTICI score of 2b or greater following the first NIMBUS pass.

   In addition, the number of subjects who achieved each mTICI category will be reported. The analysis will be stratified using the mTICI score pre the first NIMBUS pass compared to the mTICI score post the final pass of NIMBUS. The analysis will also be performed stratified using the mTICI score pre the first NIMBUS pass compared to the mTICI score post the first pass of NIMBUS.

   All mTICI scores will be based on the assessment from the Independent Core Laboratory.

4. **Occurrence of Embolization to a New Territory (ENT)**

   The occurrence of embolization to previously unaffected territory will be recorded, as evaluated from procedural imaging by the independent Imaging Core Lab. This endpoint is defined as the number and percentage of subjects with ENT following the final pass of NIMBUS. The two-sided exact 95% confidence interval will be conducted around the percentage.

5. **Symptomatic Intracerebral Hemorrhage (sICH) at 24 hours specified according to the Heidelberg Bleeding Classification (HBC)**

   sICH is defined as a new intracranial hemorrhage as detected by brain imaging, measured 24 hours after intervention. The number and percentage of subjects with sICH at 24 hours post-procedure as assessed by HBC will be summarized. The two-sided 95% confidence interval will be conducted around the percentage.

6. **90 Day All-Cause Mortality**

   The incidence of all mortality regardless of cause at 90 days post-procedure will be summarized. The two-sided exact 95% confidence interval will be conducted around the percentage.

7. **Modified Rankin Scale (mRS) of ≤ 2 at 90 days post-procedure**

   The mRS is a scale commonly used to measure the degree of disability or dependence in the daily activities in subjects following stroke or other neurologic events and is conducted by a qualified independent evaluator. It is a scale with seven categories ranging from no symptoms (score 0) to severe disability and death (score 6). The mRS scores will be collected at baseline, and 90 days post-

procedure, and if assessed, at discharge and unscheduled visits. The 90 day mRS must be performed by a qualified independent evaluator who is not part of the interventional treating team.

This endpoint is defined as the number and percentage of subjects who reached mRS score of ≤ 2 at 90 days post-procedure and will be analyzed in the mRS Analysis Set population. The two-sided exact 95% confidence interval will be conducted around the percentage.

9.7.5 Ancillary Endpoints

All analyses will be summarized using the mITT Analysis Set.

9.7.5.1 Clot Analyses

The following clot analyses will be summarized.

1. **Histopathologic analysis of clot collected**

   Composition of clot components, per pass, to be evaluated including: RBC, WBC, platelets, fibrin and other proteins, as evaluated by the independent Central Lab.

   Descriptive statistics will be presented on clot composition data.

9.7.5.2 Hospitalization Analyses

Medical Resource Utilization and Health Economics related data will be summarized, including:

1. **Hospitalization length of stay for index procedure and unscheduled re-hospitalizations.**

   The mean, median, minimum and maximum duration of hospitalization length of stay will be summarized.

2. **Healthcare resource utilization for index procedure, post-procedure and re-hospitalizations for unscheduled events.**

   The number and proportion of subjects with re-hospitalizations, and the number of hospitalizations after the index procedure will be summarized.

9.8 Handling of Missing Data

Data will be reported as available; no imputation of values is planned, except for the secondary endpoint of mRS at 90 days, where a last-observation-carried-forward will also be computed as a sensitivity analysis.

9.9 Measures to Minimize Bias

CERENOVUS will be diligent in controlling for bias by utilizing proper study design and implementation of the approved study protocol. Study agreements/contracts will be made with the hospitals/universities and all compensation for conduct of the study will be paid to the hospitals/universities and not to the investigators. Every effort will be made to obtain informed consent from consecutive eligible subjects to avoid selection bias.

An independent core laboratory will perform the angiographic assessments for the primary endpoint and the secondary endpoints associated with mTICI and ENT.

Clinical outcomes will be measured in a standardized manner using the National Institutes of Health Stroke Scale, a standardized, objective, clinical assessment tool used to quantify and document the neurological

status of patients and to act as a predictor for clinical outcomes. It is used to determine stroke and the severity of stroke.

Clinical outcomes will be measured in a standardized manner using the Modified Rankin Scale, a commonly utilized seven-point scale measuring functional outcome and disability in patients with stroke. The mRS measures independence and dependence related to activities of daily living and can be used over time to determine recovery or regression. mRS will be performed by a qualified independent evaluator who is not part of the interventional treating team.

Study monitors will have clinical research experience and be proficient at study monitoring. Study data will be source data verified (SDV) as specified in the monitoring plan using the subject's medical records, study source worksheets, clinic notes, and radiographic reports as applicable as source documentation.

10 ETHICAL AND REGULATORY CONSIDERATIONS

As the Sponsor of this study, CERENOVUS has the overall responsibility for the conduct of the study and, will ensure that the study is conducted in accordance with GCP, ISO 14155 requirements, local regulations, the signed clinical study contract with Sponsor, the protocol outlined herein, as well as with the principals of the Declaration of Helsinki.

- **General Responsibilities**

  Sponsor's general duties consist of assuring that sites have received regulatory approval where applicable, EC approvals, selecting investigators, ensuring proper clinical site monitoring and ensuring subject informed consent is obtained. Any additional requirements imposed by an EC or regulatory authority shall be followed, if appropriate.

- **Data Quality and Reporting**

  Sponsor is responsible for providing quality data that satisfy applicable regulations and informing proper authorities of unanticipated adverse effects and deviations from the protocol as applicable.

- **Selection of Investigators**

  Sponsor will select qualified investigators, obtain a signed Investigator Agreement and provide the investigators with the information necessary to conduct the study.

- **Supplemental Applications—Protocol Amendments**

  As appropriate, and where applicable, Sponsor will submit changes in the study protocol to investigators to obtain EC re-approval. A justification for each amendment will be documented.

- **Maintaining Records**

  Sponsor will maintain copies of correspondence, reportable Adverse Events and other records related to the study. Sponsor will maintain records related to the signed Investigator Agreements.

10.1 Ethics Committee

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the EC for review and approval. EC approval of both the protocol and the informed consent form must be obtained before any participant is consented. A original signed/stamped copy of the EC approval letter and approved informed consent form must be submitted to CERENOVUS certifying study approval prior to subject consent.

When required by the EC, review and approval of protocol/study material(s) amendments should be obtained from the EC before the changes are implemented at the applicable study site(s). CERENOVUS and the EC must approve in writing any changes to the protocol/study material(s) that affect the rights safety and/or welfare of the subjects or may adversely affect the validity of the study. All changes to the informed consent form will be EC approved and a determination will be made regarding whether previously consented participants need to be re-consented.

Investigators are responsible for submitting and obtaining initial and continuing review of the study by their EC.

10.2 Insurance

CERENOVUS will secure and maintain in full force and effect, throughout the duration of the Clinical study, clinical trial insurance in line with national regulations. The type of insurance for each participating site is detailed within the respective Clinical Study Contract which will be executed before the start of subject recruitment at that site.

10.3 Informed Consent and Data Release Form Process

10.3.1 Consent and Other Informational Documents Provided to Participants

Subject's informed consent must be obtained and documented in accordance with specific provisions of the associated ECs, the current applicable version of ISO 14155, the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP), and the applicable national and regional regulatory requirements. Due to the emergent nature of AIS, consent may be obtained after the procedure up to 7 days post-procedure as permitted by the local regulations and EC.

The EC must review and approve an informed consent form (ICF) specific to this study. CERENOVUS will provide each study center with an example ICF. The clinical center, to meet specific EC requirements, may modify this example ICF. Each investigational site will provide CERENOVUS with a copy of the EC approved ICF and renewed approvals and consents as appropriate for the duration of the study. The original, signed and dated ICF should be retained by the investigational site for monitoring, and a signed copy provided to the subject.

If applicable per local regional requirements, a data release form must be obtained prior to releasing subject information. The EC must review and approve the data release form specific to this study and the written data release form must be signed and dated by the subject prior to participation in this study. The original, signed and dated data release form should be retained by the investigational site for monitoring, and a copy provided to the subject.

10.3.2 Consent and Data Release Form Procedures and Documentation

Informed consent is a process that is initiated prior to an individual agreeing to participate in a study and continues throughout the individual's study participation. Risks and possible benefits of participation will be discussed with the patient and their families as requested prior to enrolment in the study and being considered a subject. The investigator, or designee, will explain the research study to the potential subject and answer any questions that may arise. All patients will receive verbal and written information in language at a level of complexity understandable to the patient about the purpose, procedures, and potential risks of the study and of their rights as research participants. Patients will have ample opportunity to review the written consent form and to ask questions prior to signing. The patients should be allowed additional

time as desired to consider the study prior to agreeing to participate. Prior to participation in the study, the Patient Informed Consent Form will be signed and personally dated by the patient or his/her legal representative. The subject may withdraw consent at any time throughout the course of the study. The rights and welfare of the participants will be protected and it will be emphasized to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. A signed and dated copy of the Patient Informed Consent Form must be collected from each enrolled subject and kept in the study subject files. Subjects will be notified in a timely manner of any significant new information that develops over the course of the study that may affect their willingness to participate.

Subject confidentiality will be maintained throughout the clinical study in a way that assures that individual subject data can be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject. Data relating to the study may be made available to third parties, provided the data are treated as confidential and that the subject's privacy is guaranteed.

As applicable per local regional requirements, a data release form may also be required and must be obtained prior to releasing patient information, if required. Similar to consenting procedures, the consent discussion should be conducted in non-technical wording understandable for the patient and the patient must have ample time and opportunity to inquire about further details.

10.4 Participant and Data Confidentiality

During this study, all representatives of the Sponsor will comply with all in-country privacy laws, and regulations regarding contact with subjects, their medical record information, copying of information, and protection of the subject identities.

All information and data sent to CERENOVUS concerning subjects or their participation in this study will be considered confidential. Only authorized CERENOVUS personnel or representatives (including contracted service providers, i.e. Imaging Core Lab, Clinical Research Associate, Central Lab etc.), representatives of regulatory agencies will have access to these confidential files upon request (including, but not limited to, admissions/discharge summaries for hospital admission occurring during a subject's study participation and autopsy reports for deaths occurring during the clinical investigation). All data used in the analysis and reporting of this evaluation will exclude identifiable reference to the subject.

10.4.1 Research Use of Stored Human Samples, Specimens and data

Clot samples and related data collected under this protocol may be used to further study the etiology of AIS. Access to stored samples and data will be limited to study related personnel, to include CERENOVUS appointed vendors. Samples and data will be stored using de-identified codes assigned to subjects. Results of the testing will remain the property of CERENOVUS.

10.5 Future Use of Stored Specimens

With the subject's consent and as approved by local EC, de-identified biological samples will be stored at the Central Labs for future analysis. These samples could be used for research into the causes of AIS and will be used until the Research and Development testing is complete or the sample is completely used. Samples not completely used will be stored for future use in stroke related research.

11 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and ongoing QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written (Standard Operating Procedures) SOPs, monitors will verify that the clinical study is conducted, and data are generated, documented, and reported in compliance with the protocol, ISO 14155, GCP, and the applicable regulatory requirements. If noncompliance is identified, Sponsor will implement measures to secure compliance.

The investigational site will provide direct access to all study related information, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Collection and Management Responsibility

Data collection is the responsibility of the site clinical study staff under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data entered. The Sponsor is responsible for all data management activities. These activities include the development of a database, utilizing validated database software, into which all study data will be entered by the clinical sites. The Sponsor will be responsible for ensuring the overall integrity of the database.

12.1.1 Electronic Case Report Forms

Electronic CRFs have been developed to capture the information outlined in this study protocol. Data on these eCRFs will be monitored, corrected if necessary, and entered into a validated database. All changes made to the data will be tracked in the electronic audit trail, recording the current value, previous value, reason for change, date timestamp of data entry/change, and the name of the person who changed the data. The investigator or designee (the designee must be another investigator on the study team) will electronically sign all subject eCRFs as verification that the data have been reviewed and correctly reflects source documentation. Data from these eCRFs will be used to provide analysis of this study.

12.1.2 Source Documentation

Data entered on to the eCRFs will be obtained from source documentation, such as hospital procedure reports, admission and discharge summaries, and other hospital or physician office/clinic documents. If no standard hospital or clinic document exists to capture information required specifically for this clinical investigation, a source worksheet may be developed to record this information. These source documents will serve as the basis for monitoring subject specific information against the eCRFs.

Electronic subject records will be considered source documents on the condition that the hospital's database is a validated system. If this is not the case, electronic records will have to be printed and added to the subject's paper file. A print-out of an eCRF cannot be used as source documentation.

12.1.3 Study Records

Regulations require that investigators maintain information in the subject's medical records, which corroborate data collected on the eCRFs. The Investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically

such as digital imaging). The Investigator will also maintain source documents from which study-related data are derived, which include, but are not limited to:

- Clinic progress notes recording subject's medical history and medications
- Medical charts with operative reports and condition of subject upon discharge
- Medical records regarding device and procedure related Serious Adverse Events, including treatment and clinical outcome
- Results of diagnostic examinations
- Imaging (such as CTs, MRIs, Angiography), as well as the report of the radiologist's reading/interpretation of diagnostic imaging
- Shipping records and traceability for clots sent for histopathological analysis
- Notes of phone calls and/or correspondence indicating investigational site's attempts to follow study subjects at the required follow-up visits until subject's participation in the study is complete or terminated
- Records relating to subject death (e.g., death certificate, autopsy report)
- Print-outs of source data generated by technical equipment (e.g., x-rays, MRIs) must be filed with the subject's records.

Only authorized CERENOVUS personnel or representatives, authorized site personnel, and local government authorities, will have access to these confidential files.

12.1.4 Health Economic Data

Subject hospitalization information will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Subject admission and discharge date will be collected for the index procedure. Re-hospitalization data for unscheduled events will include admission and discharge date and primary diagnosis, and all procedures performed during re-admission.

12.1.5 Data Reporting

The investigator, or designated individual, is responsible for timely completion of all data from the study via the eCRFs supplied by CERENOVUS. The investigator/delegated individual is required to electronically sign the eCRF on the appropriate pages to verify that he/she has reviewed, and attests to the correctness, of the recorded data. Completed eCRFs will be reviewed and monitored at the investigational site by CERENOVUS, personnel or designee at regular intervals throughout the study. To this end, the investigator and institution must permit inspection of the study files and subject eCRFs by such representatives and/or responsible government agencies.

Investigators are required to prepare and submit accurate and timely reports on this study to the EC and CERENOVUS as applicable.

12.1.6 Data Verification and Review

CERENOVUS will track the amount of missing data and contact sites as appropriate to instruct them on steps to minimize missing data and remain compliant with protocol required assessments. Missing or unclear data will be queried as necessary throughout the study. CERENOVUS will request further

documentation such as physician and/or radiology reports when complications or malfunctions are observed and reported. CERENOVUS will be responsible for auditing the database and confirming the overall integrity of the data.

12.1.7 Final Data Analysis

All exported datasets for analyses will undergo a final data review before final database lock. Once all critical data are monitored and locked, the final analyses of clinical investigation data will be performed.

12.1.8 Study Record Retention and Archiving

The sponsor and principal investigator shall maintain the clinical investigation documents as required by the applicable regulatory requirement(s). They shall take measures to prevent accidental or premature destruction of these documents. The principal investigator or sponsor may transfer custody of records to another person/party and document the transfer at the investigation site or at the sponsor's facility. It is the Investigator's responsibility to retain study essential documents and source documentation that support the data collected on the study subjects for a period as defined by local requirements. These documents may be retained for a longer period if required by local laws and/or an agreement with CERENOVUS. Prior to disposal of any records, the Investigator should notify CERENOVUS. The investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. CERENOVUS must receive written notification of this custodial change.

Each site must maintain a file of all documents and records relating to the conduct of this study that will include but will not be limited to the following documents:

- A copy of the Protocol and each Amendment (if applicable);
- EC Approval(s) and Continuing Review (when applicable) for the Protocol, Protocol Amendment(s) and study ICF(s);
- EC approved ICF(s) template;
- EC and Sponsor Correspondence, including Reports;
- Clinical Study Contract, fully executed;
- Principal Investigator, Sub-investigator(s), site personal Curriculum Vitae;
- Protocol Signature Page(s);
- Site Training Records;
- Study Personnel Authorization Form (Site Delegation Log);
- Screening and Enrolment Log, if applicable;
- Subject Identification Log (not to be removed from site);
- IFU;
- ICFs for each subject enrolled (not to be removed from site).

Only authorized CERENOVUS personnel or representatives, authorized site personnel, and local government authorities, will have access to these confidential files.

13 PROTOCOL DEVIATIONS

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures described in the protocol, and any conditions required by the reviewing EC. A protocol deviation is a failure to comply (intentionally or unintentionally) with the requirements of the clinical study

as specified in the protocol. Examples of protocol deviations include late visits, missed visits, required follow-up testing not completed, visit out of window, non-adherence to inclusion/exclusion criteria, etc. and shall be reported to the Sponsor through the eCRFs. Deviations will be reviewed and assessed by the Sponsor.

It is the responsibility of the site to use vigilance to identify and report deviations to the Sponsor and EC per guidelines. The study monitors shall verify that the conduct of the study is in compliance with the approved protocol and applicable regulations and shall identify deviations and any issues of noncompliance. Corrective and preventative actions will be implemented promptly as necessary and significant protocol deviations that raise subject safety concerns or indicate repeat noncompliance may be grounds for investigator disqualification and/or reporting to the regulatory authorities.

The investigator is not allowed to deviate from the protocol except under emergency circumstances to protect the rights, safety and well-being of study participants. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the ethics committee. Such deviations shall be documented and reported to the sponsor and ethics committee as soon as possible.

14 STUDY ADMINISTRATION

14.1 Study Registration

This study will be registered on the clinical trial registries and results data banks like, but not limited to www.ClinicalTrials.gov.

14.2 Steering Committee

A Steering Committee of experts with experience in the areas of neurosurgery, neurology or interventional neuroradiology will be appointed for this study. The responsibilities of the Steering Committee include:

- Consultation on study design, protocol development, patient eligibility inquiries, data to be collected and investigator training.
- Study oversight including safety
- Review of evidence results (assist in data interpretation).

15 DATA AND PUBLICATION POLICIES

Publications and/or presentation of the clinical investigational results will be coordinated between CERENOVUS and the clinical investigation author(s). Authorship will be determined prior to development of any manuscript. All information concerning the study device, Sponsor operations, patent application, manufacturing processes, and basic scientific data supplied by the Sponsor to the investigator and not previously published, are considered confidential and remain the sole property of the Sponsor.

16 CONFLICT OF INTEREST

The term “conflict of interest” refers to situations in which financial or other personal considerations may compromise or have the appearance of compromising a researcher's professional judgment in conducting or reporting research. CERENOVUS will make every effort to safeguard against conflicts of interest to assure the integrity of the data, subject safety and investigator objectivity.

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