Clotild® Smart Guidewire System evaluation in Endovascular Thrombectomy procedure

Study name	**CLOT OUT**
Protocol Number	**SEN_CLOTILD_FIH_1**
Version	**6**
Date	**12 June 2023**

CLINICAL INVESTIGATION PLAN

	Name	Function	Date/Signature
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Version	Change*	
1	Creation	
2	Revision	Information added on request of Ethics Committee (Australia)
3	Revision	Protocol adjusted to ensure EU specific information is incorporated
4	Revision	Protocol adjusted on request of French Regulatory Agency, ANSM
5	Revision	Protocol adjusted to ensure compliance with FDA recommendations
6	Revision	Protocol adjusted to revise sample size calculation / statistical methodology and clarify study procedure definition.

* Detailed descriptions of and rational for changes can be found in Annex 1 of this protocol.

TABLE OF CONTENTS

1 SPONSOR APPROVAL PAGE

We confirm that this Clinical Investigation Plan (CIP) has been reviewed by medical doctors, experts in the field of neuroradiology. Moreover, this CIP is conformed to the applicable regulatory guidelines, including the Declaration of Helsinki (October 2013), the ISO 14155 (2020) and the applicable regulatory authority requirements of the countries in which this clinical investigation will take place.

Signature and date:	Signature and date:
Franz Bozsak President	Hans Tielemans Clinical Expert
Signature and date:	Signature and date:
Andrew Cheung, MD Coordinating Investigator	Dennis Cordato, MD Coordinating Investigator

2 STATEMENT OF COMPLIANCE

I confirm that this study will be conducted in compliance with the Clinical Protocol, Informed Consent, Instructions for Use, Investigator's Brochure, and all other associated documents in adherence with the latest version of the Declaration of Helsinki (October 2013), the international standard ISO 14155: (2020) ('Clinical Investigation of medical devices for human subjects'), and all applicable regulatory authority requirements state and national laws. In case of conflicting requirements, the regulation affording the greatest protection to the subject will be followed.

I have sufficient time to properly conduct and complete the trial within the agreed trial period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

Principal Investigator's Name	Site Name
Principal Investigator's Signature	Date of signature

3 STUDY CONTACTS

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4 LIST OF ABBREVIATIONS

Term	Definition
ADE	Adverse Device Effect
AE	Adverse event
AUC	Area Under the Curve
BLE	Bluetooth Low Energy
CA	Competent Authorities
CIP	Clinical Investigation Plan
CSGS	Clotild® Smart Guidewire System
CT scan	Computed Tomography Scan
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EVT	Endovascular Thrombectomy
IB	Investigator's Brochure
INR	Interventional Neuroradiologist
LAR	Legally Authorized Representative
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
mTICI	modified Treatment In Cerebral Ischemia
NIHSS	National Institutes of Health Stroke Scale
OEM	Original Equipment Manufacturer
PICF	Patient Information and Consent Form
RBC	Red Blood Cells
ROC	Receiver Operator Characteristic
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SGW	Smart GuideWire
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect

5 STUDY SUMMARY

Title	CLOT OUT (Clotild® Smart Guidewire System evaluation in Endovascular Thrombectomy procedure)
Protocol Number	SEN_CLOTILD_FIH_1
Study Device	Clotild® Smart Guidewire System (CSGS)
Purpose	The objective of the study device is to evaluate the safety and ability of Clotild® Smart Guidewire System to provide electrophysiological measurements. The electrophysiological measurements will be used to update CSGS's database and thus improve the prediction accuracy of the model in providing physicians with insights for treating ischemic stroke.
Study type	First-In-Human
Study design	Prospective, Multicenter, Single-arm study
Number of patients and Clinical Sites	Up to 42 patients at up to five Australian and up to eight European Centres
Patient Population	Subjects presenting with acute ischemic stroke due to an occlusion with origin in the M1 and eligible for EVT based on neuro-interventionist and/or neurologist investigators' opinion. Up to 42 patients will be enrolled following an analysis of the data of the first 20 enrolled patients by a Data Safety Monitoring Board (DSMB) and its recommendation to proceed with the study. DSMB review is planned at 5 and 20 patients, all centers combined, and the final review after the last patient has been enrolled.
Endpoints	**PRIMARY ENDPOINTS** **Primary Safety Endpoint** The Primary Safety Endpoint is defined as the proportion of patients having intracranial vessel perforation and / or dissection due to Clotild® Smart Guidewire usage at the site of usage in intracranial vessels.

Primary Performance Endpoint

The Primary Performance Endpoint is defined as the ability to perform binary classification of individual electrophysiological parameter measurements (**local scale**) by distinguishing local regions with substantial red blood cell content (**RBC-positive**) from regions with negligible red blood cell content (**RBC-negative**) in the occlusion.

SECONDARY ENDPOINTS

The Secondary Endpoints are:

1. The concordance between aggregated occlusion measurements (clot scale) done by CSGS, and the histopathology results of the clot retrieved during the EVT procedure, regarding red blood cell content in the occlusion.
2. The ability of CSGS detecting the proximal end of the occlusion (sensor-scale), as compared to the physician's labelling.
3. Procedural success defined as the ability to navigate CSGS to the occlusion site and measure electrophysiological properties of the occlusion.
4. The ability to perform binary classification of individual electrophysiological parameter measurements (local scale) by distinguishing local regions with substantial platelet content (platelet-positive) from regions with negligible platelet content (platelet-negative) in the occlusion.
5. The concordance between aggregated occlusion measurements (clot scale) done by CSGS, and the histopathology results of the clot retrieved during the EVT procedure, regarding platelet content in the occlusion.
6. The ability to perform binary classification of individual electrophysiological parameter measurements (local scale) by distinguishing local regions with substantial fibrin content (fibrin-positive) from regions with negligible fibrin content (fibrin-negative) in the occlusion.
7. The concordance between aggregated occlusion measurements (clot scale) done by CSGS, and the histopathology results of the clot retrieved during the EVT procedure, regarding fibrin content in the occlusion.

TERTIAIRY ENDPOINTS

Other endpoints are more exploratory by assessing the correlation between the CSGS measurements with intervention parameters such as:

1. The arterial wall detection for individual measurement
2. The ability of CSGS detecting the distal end of the occlusion
3. The ability of CSGS predicting the number of thrombectomy passes
4. The ability of CSGS predicting the first pass effect
5. The ability of CSGS predicting the etiology of the clot
6. The ability of CSGS predicting the type of device(s) with better chances to remove the clot.

Eligibility criteria	**Inclusion criteria** Candidates for the study must meet ALL the following inclusion criteria: 1. Age ≥ 18 years. 2. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke eligible for EVT based on neurointerventionist and/or neurologist investigators' opinion. 3. Occlusion with origin in M1 on CTA or MRA of an intracranial vessel amenable to EVT. Patients with migrated clots outside M1 will not be treated with the study device. 4. Written Informed Consent to participate in the study. If the subject is incapable of providing consent due to the patient's condition and the urgency of the EVT procedure, the Informed Consent Form will be obtained as per local country practice and approved by the Ethics Committee and Regulatory Agencies (if applicable). **Exclusion criteria** Candidates for this study will be excluded if ANY of the following conditions are present: 1. Patient has an intracranial occlusion that does not originate in M1 or/and tandem occlusions. 2. Current participation in another investigational device or drug study that has not completed the primary endpoint or that clinically interferes with the current study endpoints. 3. Candidates not eligible for EVT based on neurointerventionist and/or neurologist investigators' opinion. 4. Known lactating or confirmation of positive pregnancy test according to site specific standard of care (e.g. test, verbal communication).
Estimated Study Duration	**Total study duration:** Up to 36 months ± 2 weeks subject enrolment. **Follow-up duration** Per patient basis: 24hrs (range 16-36 hrs.) post-procedure

6 INTRODUCTION

6.1 PURPOSE

The objective of the study is to evaluate the safety and the ability of Clotild® Smart Guidewire System (CSGS) to provide electrophysiological measurements. The electrophysiological measurements will be used to update CSGS's database and thus improve the prediction accuracy of the models in providing physicians with insights for Acute Ischemic Stroke (AIS) treatment.

6.2 MEDICAL BACKGROUND

Occlusion of a cerebral artery by a thrombus results in AIS. Ischemic Stroke is one of the leading causes of death among people aged over 60 years as estimated by the World Health Organization. Stroke is also responsible for long-term disability worldwide (Snow 2016).

Treatment of AIS aims to recanalize the occluded artery, promptly and efficiently, either by intravenous thrombolysis via recombinant tissue plasminogen activator (r-tPA) or mechanical removal of the thrombus via endovascular thrombectomy (EVT). In most countries, less than 15% of AIS patients are able to avail r-tPA treatment (Aguiar de Sousa et al. 2019; Hassankhani et al. 2019; Nielsen et al. 2020; Zhang et al. 2019) as it must be administered within 4.5 hours of stroke onset to minimise risk of cerebral hemorrhage. Of those who are treated with r-tPA, successful reperfusion is achieved in less than half of cases (Prabhakaran, Ruff, and Bernstein 2015; Vanacker et al. 2015). The reperfusion failure has been attributed to factors such as excess thrombus burden or inadequate dose of thrombolytic drug; aged thrombus; thrombus location; thrombolytic drug resistance (Marshall 2015). Mechanical thrombectomy is becoming more mainstream, although it is only available in stroke centres with trained Interventional Neuroradiologists. With mechanical thrombectomy, successful recanalization is attained in about 80% of cases (Zaidat et al. 2018; Mokin et al. 2020; Wollenweber et al. 2019). The reasons behind the failure of recanalization in some patients are not fully understood. Other than vascular access, composition of thrombus is likely to be an important factor (Staessens et al. 2020). Knowledge of thrombus composition in advance of treatment could direct the choice of treatment for better outcome (De Meyer et al. 2017). Although, thrombus composition and characteristics are not, at present considered to any great extent in treatment decision making, better understanding of the thrombus prior to intervention could help in achieving successful recanalization and reduce adverse secondary events via selection of appropriate thrombolytic and/or endovascular strategy for intervention.

6.3 STROKE MANAGEMENT

Endovascular thrombectomy has only been recently developed and has shown efficacy up to 8 hours after symptom onset (and under certain conditions up to 24 hours) (Jovin et al. 2017) while intravenous thrombolysis (IVT) can be used in subjects presenting up to 4.5 hours after symptom onset.

The efficacy of mechanical thrombectomy has now been established, and is largely adopted (Elgendy et al. 2015; Pereira et al. 2015) for the treatment of acute ischemic stroke, in combination with IVT (r-tPA) or as a stand-alone treatment. Current recanalization strategies attempt to establish revascularization as quickly as possible so that neurovascular cells can be rescued before irreversible injury occurs. It is established that reperfusion time can mitigate the effects of ischemia only if performed quickly (Fransen et al. 2016): medical staff must act rapidly without fragmenting the occlusion (potentially leading to embolization).

Physicians today have a choice of two technical options to mechanically retrieve the occlusion obstructing the artery: aspiration catheter or stent-retriever. None of the available devices have recorded a proven superiority in clot-removing performance. However, recanalization is not obtained in about 20% of cases and time from groin puncture to reperfusion can take up to 60 minutes (Zaidat et al. 2018; Mokin et al. 2020; Wollenweber et al. 2019). Both approaches require the use of a guidewire that is inserted and guides the catheters to the occlusion location.

Recent studies have provided preliminary data indicating that the nature of the occlusion can influence the occlusion's retrievability. Indeed, it has been demonstrated that thrombectomy strategies (choice of the first EVT device or sequence of devices chosen) success depend on the length and composition (red/white/mixed cells) of the occlusion responsible for the vessel obstruction (De Meyer et al. 2017). This explains why physicians are seeking methods to characterize clot type and predict procedure outcome through MRI (Romain Bourcier et al. 2017; R. Bourcier et al. 2017). However, CT and MRI imaging do not provide detailed information about the clot and are only performed before the intervention, so physicians are not provided with updated information during the procedure. Therefore, there is a need for physicians to know the type of occlusion blocking the artery.

In order to decrease intervention times, while minimizing the risk of embolization, SENSOME has developed a guidewire equipped with sensors, Clotild® Smart Guidewire System, providing the operating physician with information on the nature of the clot. The guidewire is the first device to reach the vessel occlusion during endovascular intervention. Due to its very flexible design, it is used, as its name suggests, to guide other interventional devices to the site of the occlusion.

By analyzing clot composition, CSGS will provide physicians with information on the thrombus and will allow them to make informed choices as to the most effective solution for mechanical thrombectomy.

7 BENCHMARK OF COMPARABLE DEVICES

Since the Clotild® Smart Guidewire (CSG) is a standard guidewire equipped with impedance sensors, comparable devices include standard guidewires, as well as catheters with embedded electronics.

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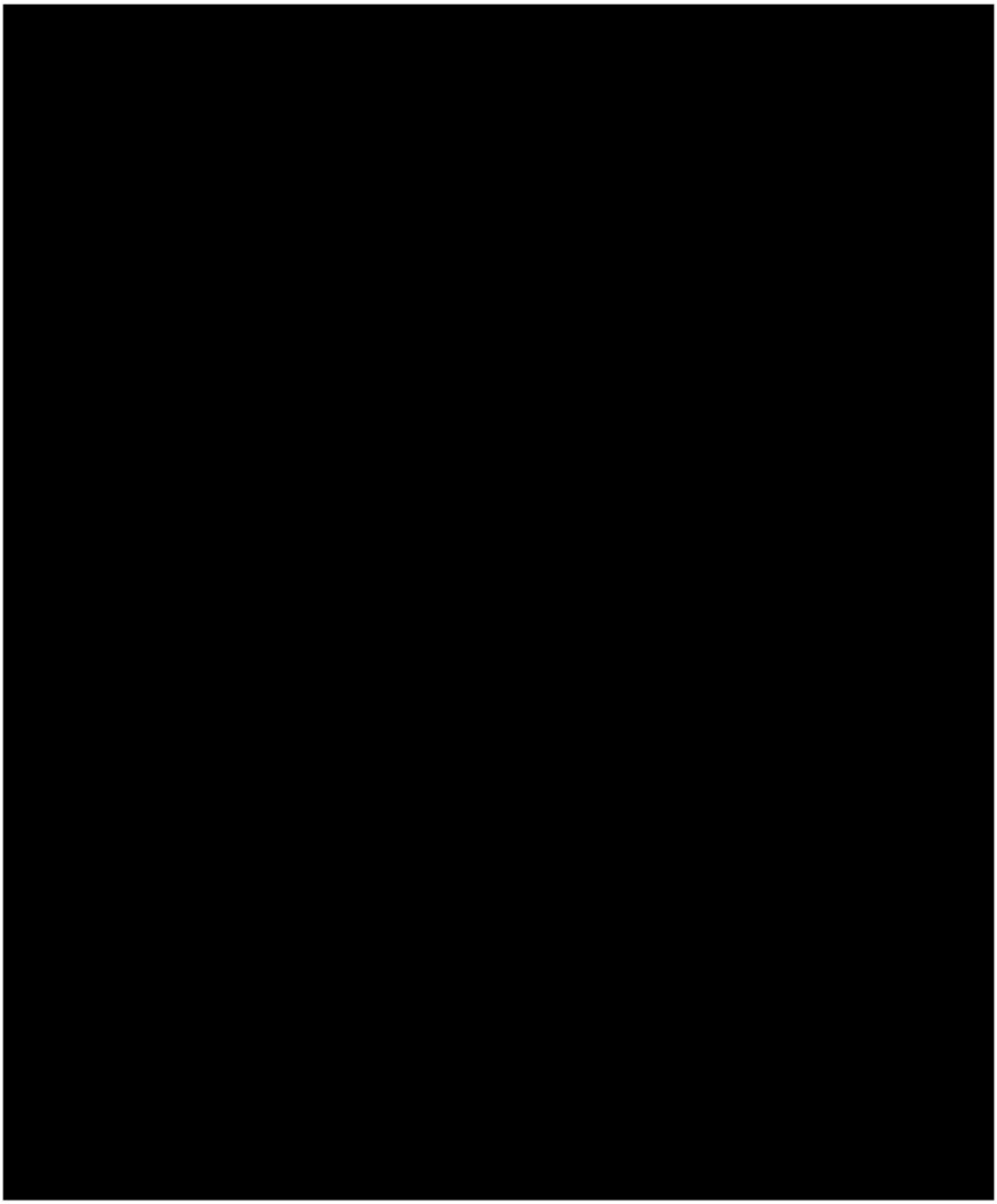

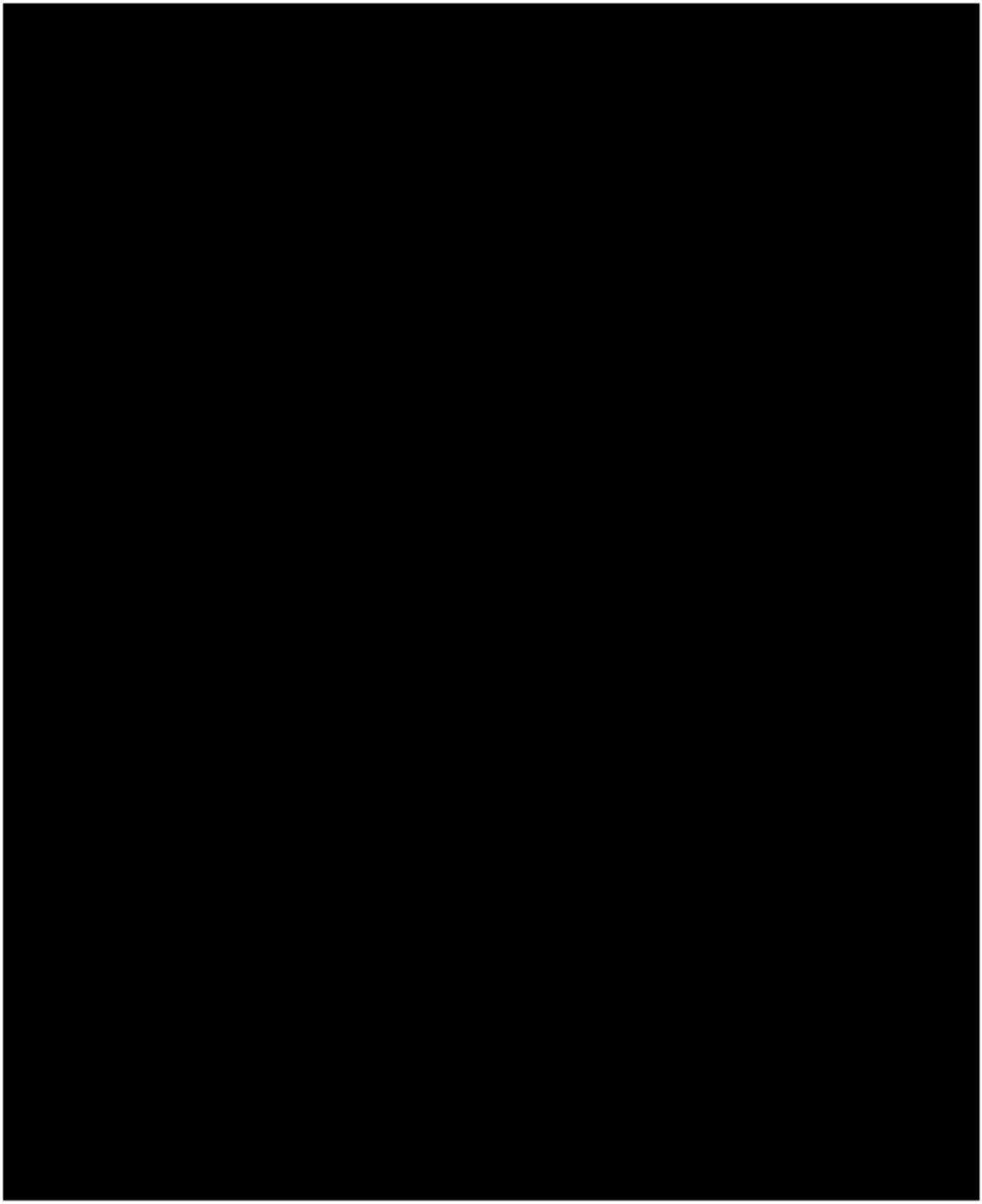

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8 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Throughout this document, 'electrophysiological parameters measurements', 'electrophysiological measurements' and 'impedance measurements' are used interchangeably.

8.1 GENERAL DESCRIPTION OF THE INVESTIGATIONAL DEVICE AND ITS COMPONENTS

Clotild® Smart Guidewire (CSGS) is a neurovascular guidewire equipped with SENSOME's proprietary impedance sensor. The latter allows the measurement of electrophysiological characteristics of the surrounding fluid or tissue. The CSGS mechanical design is broadly inspired by existing and widely used neurovascular guidewires to ensure the closest possible mechanical performance to what physicians are used to.

The complete CSGS is composed of two main sub-systems (Figure 1):

- Clotild® Smart Guidewire with its transmitter and standard accessories: a torquer and a blunt insertion needle. All these sterile parts are for single use only.
- User interface that is provided via a dedicated medical tablet that is equipped with a BLE (Bluetooth Low Energy) dongle to communicate with the transmitter. A proprietary application (Cloviz®) is running on the tablet to ensure interaction with the sensor, signal processing, and data storage.

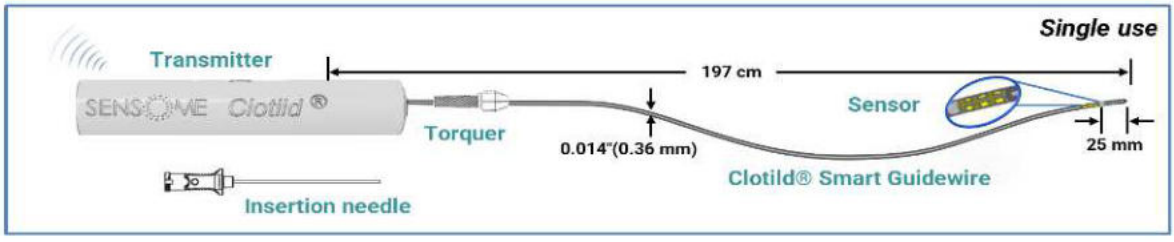

FIGURE 1: CLOTILD® SMART GUIDEWIRE SYSTEM OVERVIEW

8.1.1 Clotild® Smart Guidewire

The guidewire has a standard 0.014'' (0.36 mm) diameter and 2 m length. As mentioned above, its mechanical design was widely inspired by existing state of the art commercial guidewires.

FIGURE 2 SCHEMATIC VIEW OF THE CLOTILD® SMART GUIDEWIRE'S CROSS-SECTION

The sensor is composed of 3 rows of electrodes with 3 electrodes per row, totalling 9 electrodes. An electrophysiological measurement is performed between a pair of two electrodes. Thus, the sensor can perform 3 measurements in between the 3 pairs of electrodes per row, so a total of 9 measurements for the entire sensor. These individual impedance measurements at the scale of a single electrode pair are defined as the '**local scale**'. The aggregation of the 9 individual measurements, consisting in a full acquisition by the sensor, is defined as the '**sensor scale**'. When several

measurements are performed all along the occlusion, the aggregation of all measurements is defined as the '**clot scale**'.

Figure 3: Schematic view of the sensor presenting the different scales of measurements.

8.1.2 Transmitter

The transmitter is connected to the guidewire through the rings of the proximal connector. The proximal part of the guidewire is inserted into the female connector of the transmitter.

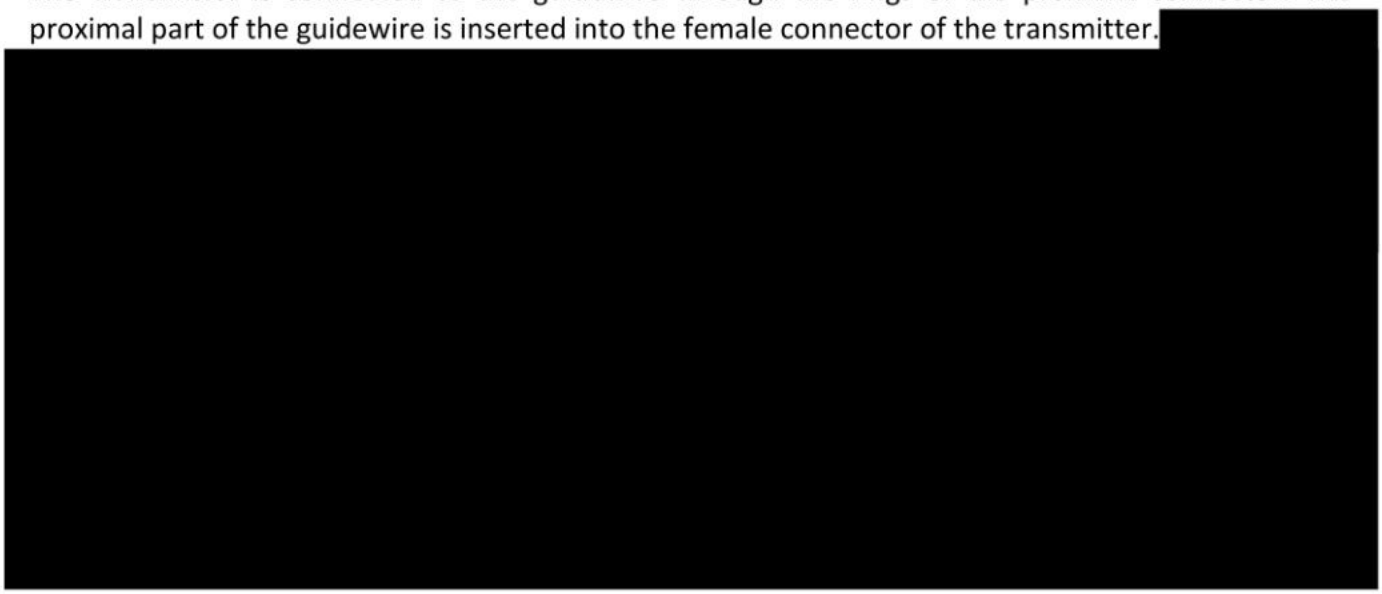

FIGURE 4 CLOTILD® SMART GUIDEWIRE TRANSMITTER

8.1.3 User Interface

All the interactions with the guidewire sensor are performed through the touchscreen medical tablet carrying proprietary application Cloviz® software (FIGURE 5). The tablet is supplied with a Bluetooth USB dongle that provides wireless communication with the transmitter.

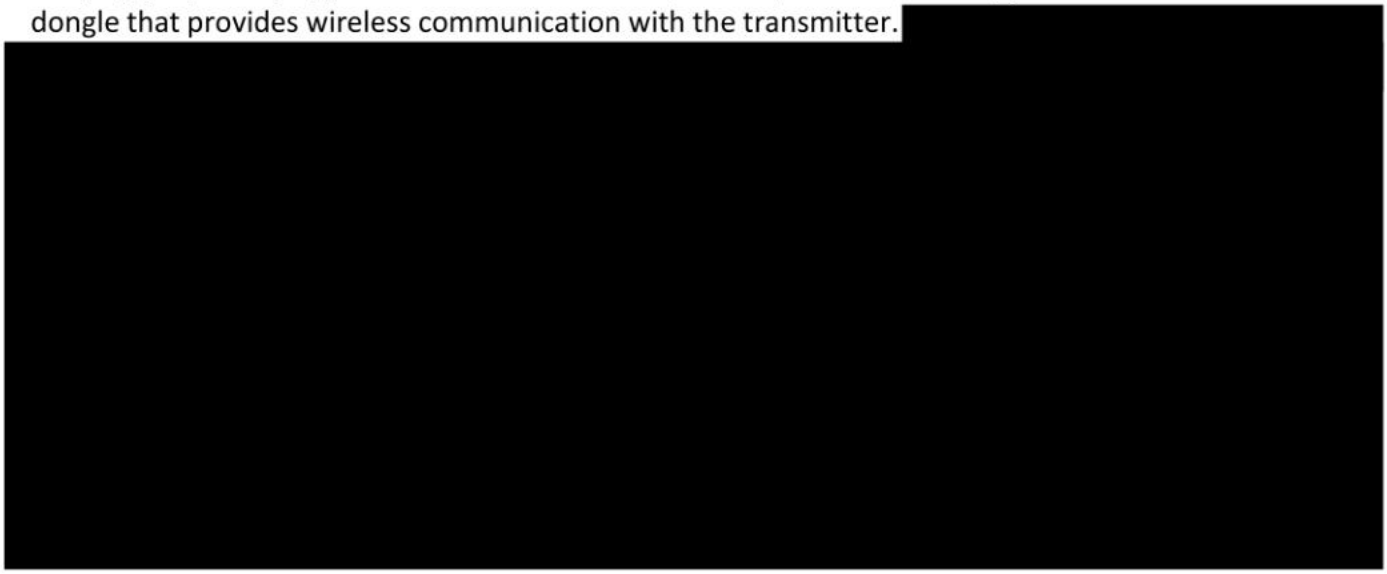

FIGURE 5 MEDICAL TABLET WITH CLOVIZ® SOFTWARE

8.2 INTENDED USE

Intended Use

Clotild® Smart Guidewire System is indicated to direct a catheter through blood vessels and to measure electrophysiological parameters in the blood vessels during diagnostic or interventional procedures.

Indication of Use

Clotild® Smart Guidewire System is indicated for neurovascular use. It can be used to facilitate introduction of diagnostic and therapeutic devices, as well as to measure electrophysiological parameters in blood vessels.

8.3 DEVICE ACCOUNTABILITY AND STORAGE

The investigator is responsible for the device accountability at the trial site. The investigator may assign some of the duties for device accountability at the trial site to an appropriate staff member.

Upon receipt of an investigational device shipment, the Investigator or designee is required to reconcile inventory of the product received and verify the shipment by signing the Delivery Note. All investigational devices must be stored in a locked storage facility to which only the investigator, and/or designated assistants will have access following the recommendation provided by SENSOME either on the device's label or IFU.

Devices under investigation will be labelled "Exclusively for Clinical Investigations" and only used in the clinical investigation and according to the protocol. To ensure device's traceability throughout the

study, the investigational devices are identified using the unique device identification (UDI) system that contains product data, as GTIN number, lot number, serial number and expiry date.

Access to and use of the devices will be controlled and documented in the device accountability log with the following information:

- Date of receipt (if device is pending marketing approval)
- Serial number and/or batch number
- Expiry date
- Date of use
- Subject study identification number
- Date of return, if applicable

Records will track the physical location of the investigational devices from shipment to investigation sites until return or disposal. In particular, delivery slips and acknowledgment of receipts will be filed in the Investigator Site File.

8.3.1 Device Return

Used study devices will be returned to SENSOME. The sponsor will provide instructions and shipping materials.

All unused study devices will be returned upon the request of SENSOME.

For any study device/s with a reported device deficiency/device malfunction, the device should be secured in a biohazard bag to send back to manufacturer for investigation/analysis.

8.4 PRE-CLINICAL TESTING

In order to provide evidence that the device under study is sufficiently safe and performant for early human experience, animal studies were conducted.

The experiments were performed in a swine model tested and validated in a feasibility study. It combined a model of tortuous anatomy for navigability evaluation and a stroke model with autologous occlusions of controlled composition (fibrin-rich occlusions, RBC-rich occlusions, and occlusions combining fibrin-rich and RBC-rich zones).

The tested devices underwent the same manufacturing process, including coating, packaging and sterilization as the processes expected for the commercial Clotild® Smart Guidewire System. For this reason, the tested devices were representative of the devices that will be used for the FIH trial.

8.4.1 Relevance of the animal model

8.4.2 Conclusion

[redacted]

9 STUDY DESIGN AND POPULATION

9.1 STUDY DESIGN

This study is a prospective multi-centre, single-arm study to evaluate the safety and the performance of Clotild® Smart Guidewire System during endovascular thrombectomy (EVT) procedures, in subjects presenting AIS.

Patients will be enrolled in up to five (5) Australian and up to eight (8) European centres.

Up to 42 patients will be enrolled following an analysis of the data of the first 20 enrolled patients by a Data Safety Monitoring Board (DSMB) and its recommendation to proceed with the study.

Subjects will be selected as per the inclusion/exclusion criteria of the protocol and as per indications for EVT and interventional neuroradiologist and neurologist investigators' opinion. All EVT procedures will be executed as per the IFU for the corresponding device(s) and using the Clotild® Smart Guidewire System.

9.2 ELIGIBILITY CRITERIA

9.2.1 Inclusion criteria

Candidates for the study must meet ALL the following inclusion criteria:

1. Age ≥ 18 years.
2. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke eligible for EVT based on neurointerventionist and/or neurologist investigators' opinion.
3. Occlusion with origin in M1 on CTA or MRA of an intracranial vessel amenable to EVT.
4. Written Informed Consent to participate in the study. If the subject is incapable of providing consent due to the patient's condition and the urgency of the EVT procedure, the Informed

Consent Form will be obtained as per local country practice and approved by the Ethics Committee and Regulatory Agencies (if appl.).

9.2.2 Exclusion criteria

Candidates for this study will be excluded if ANY of the following conditions are present:

1. Patient has an intracranial occlusion that does not originate in M1 or/and tandem occlusions.
2. Current participation in another investigational device or drug study that has not completed the primary endpoint or that clinically interferes with the current study endpoints.
3. Candidates not eligible for EVT based on neurointerventionist and/or neurologist investigators' opinion.
4. Known lactating or confirmation of positive pregnancy test according to site specific standard of care (e.g. test, verbal communication).

10 STUDY OBJECTIVES

10.1 PRIMARY OBJECTIVE

The Primary objective of the study is to evaluate the safety of using Clotild® Smart Guidewire System (CSGS) at the occlusion location during an EVT procedure for the treatment of subjects with acute ischemic stroke eligible for EVT.

10.2 SECONDARY OBJECTIVE

The secondary objective of the study is to evaluate the performance of CSGS, defined here as the feasibility to measure electrophysiological properties of the occlusion in vivo during EVT procedures for the treatment of acute ischemic stroke.

10.3 TERTIARY OBJECTIVES

The tertiary objective of the study is to explore possible relationships between CSGS measurements and intervention parameters such as first pass effect, number of passes to successfully retrieve the clot and other key parameters. Due to the nature of the tertiary objectives, not all centers may contribute to the data collection.

11 STUDY ENDPOINTS

11.1 PRIMARY ENDPOINTS

11.1.1 Primary Safety Endpoint

The **Primary Safety Endpoint** is defined as the proportion of patients having intracranial vessel perforation and/or dissection due to CSGS usage at the site of usage in intracranial vessels by assessment by Interventional Neuroradiologist during the procedure and final adjudication of the DSA (Digital Subtraction Angiography) by the Data Safety Monitoring Board. The primary safety endpoint will be determined in all patients for whom the guidewire went through the introduction sheath.

11.1.2 Primary Performance Endpoint

The **Primary Performance Endpoint** is defined as the ability to perform binary classification of individual electrophysiological parameter measurements (**local scale**) by distinguishing local regions with substantial red blood cell content (**RBC-positive**) from regions with negligible red blood cell content (**RBC-negative**) in the occlusion.

11.2 SECONDARY ENDPOINTS

The Secondary Endpoints are:

1. The concordance between aggregated occlusion measurements (**clot scale**) done by CSGS, and the histopathology results of the clot retrieved during the EVT procedure, regarding **red blood cell content** in the occlusion.
2. The ability of CSGS detecting the **proximal end of the occlusion** (sensor-scale), as compared to the physician's labelling (tag 'PRE-CLOT' for no occlusion contact and tag 'CLOT' for occlusion contact).
3. **Procedural success** defined as the ability to navigate CSGS to the occlusion site and measure electrophysiological properties of the occlusion.
4. The ability to perform binary classification of individual electrophysiological parameter measurements (**local scale**) by distinguishing local regions with substantial platelet content (**platelet-positive**) from regions with negligible platelet content (**platelet-negative**) in the occlusion.
5. The concordance between aggregated occlusion measurements (**clot scale**) done by CSGS, and the histopathology results of the clot retrieved during the EVT procedure, regarding **platelet content** in the occlusion.
6. The ability to perform binary classification of individual electrophysiological parameter measurements (**local scale**) by distinguishing local regions with substantial fibrin content (**fibrin-positive**) from regions with negligible fibrin content (**fibrin-negative**) in the occlusion.

7. The concordance between aggregated occlusion measurements (**clot scale**) done by CSGS, and the histopathology results of the clot retrieved during the EVT procedure, regarding **fibrin content** in the occlusion.

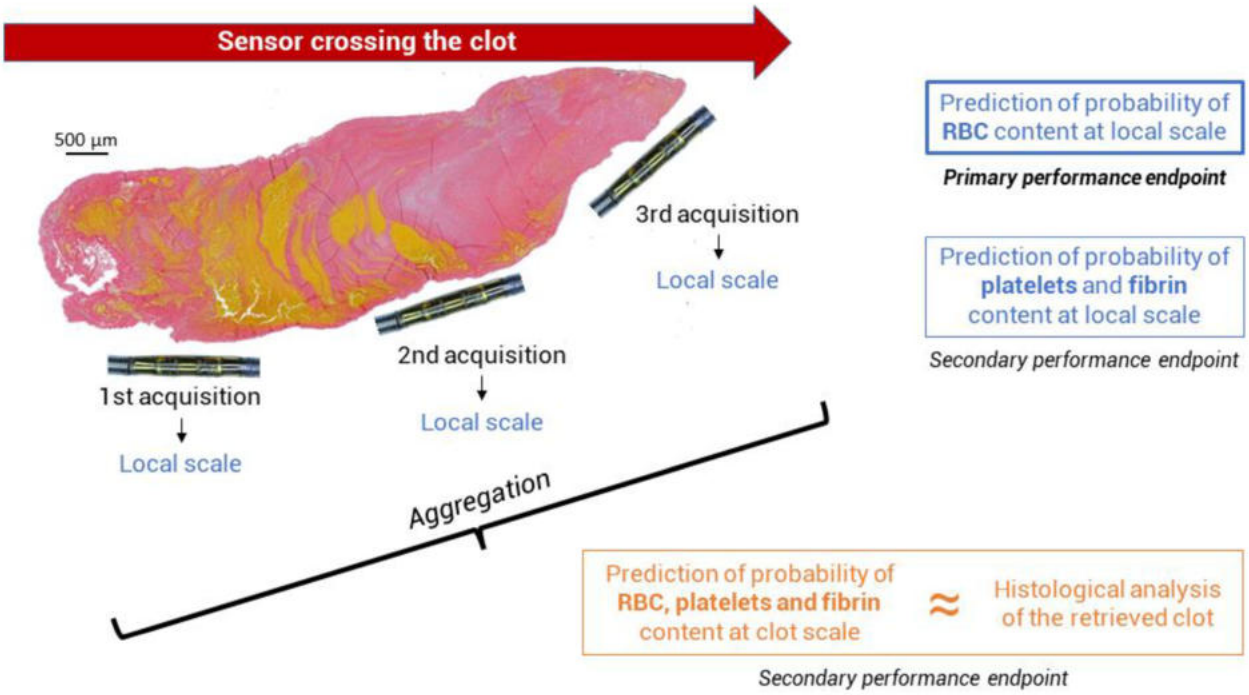

Figure 6: Schematic view of Primary and Secondary Performance Endpoints

11.3 TERTIARY ENDPOINTS

Other endpoints are more exploratory by assessing the correlation between the CSGS measurements with intervention outcomes such as:

1. The arterial wall detection for individual measurements, specifically the local detection of arterial wall vs. clot when clot-contact is ensured.
2. The ability of CSGS detecting the distal end of the occlusion.
3. The ability of CSGS predicting the number of thrombectomy passes.
4. The ability of CSGS predicting the first pass effect i.e. patients in whom the clot was removed on the first pass with a TICI score of 2c or 3.
5. The ability of CSGS predicting the etiology of the clot.
6. The ability of CSGS predicting the type of device(s) with better chances to remove the clot.

12 RISK ANALYSIS

Risk assessment is an integral part of the Sponsor's Design Control process and follows the requirements specified in EN/ISO 14971:2019 – Application of Risk Management to Medical Devices. As part of the CSGS device product development process, formal risk analyses regarding the design and the use of the device were performed. Based on the results of these risk analyses and the nature of the risks identified, performance requirements were specified, and an appropriate safety plan was developed to verify that the specified requirements have been met. This process mitigates the overall risks associated with the investigational device as extensively as possible.

12.1 RISKS ASSOCIATED WITH THE USE OF A COMMERCIALLY AVAILABLE GUIDEWIRE

Potential complications encountered when using the guidewire include but may not be limited to:

- Vascular perforation, dissection or other damage to the vessel wall
- Vascular spasm
- Thrombus formation proximal, adjacent or distal to the initial occlusion site
- Vessel rupture
- Embolization to new territory
- Haemorrhage, including subarachnoid hemorrhage from vessel injury
- Haemorrhagic transformation of the treated stroke
- Death of any cause
- Device failure (intra-procedural breakage)
- Allergic reaction

12.2 RISKS ASSOCIATED WITH THROMBECTOMY PROCEDURES

The following adverse events may possibly be caused by, or associated with the thrombectomy procedure.

- Adverse reaction to antiplatelet, anticoagulation agents, contrast media or other medication used in the procedure, or device material
- Air embolism
- Arteriovenous fistula
- Occlusion fragmentation / detachment
- Death
- Deterioration of neurological status
- Device(s) deformation, collapse, fracture or malfunction
- Distal embolization including to a previously uninvolved territory
- Haematoma and haemorrhage at puncture site
- Infection
- Intracranial hemorrhage
- Failure to withdraw/deploy the device or remove the occlusion (technical success)
- Perforation or dissection of the vessel (vessel injury)

- Pseudo aneurysm formation
- Stroke / reoccurring stroke
- Thrombosis (acute and subacute)
- Vascular spasm

12.3 RISK MINIMIZATION

12.3.1.1 Pre-clinical risk minimization

SENSOME has implemented a risk management process according to the EN ISO 14971:2019 and is documented in a Risk Management file within the SENSOME Quality System. The risk management methodology is described in *SEN_QRM_SOP_1001* (Quality Risk Management Process) and it consists in defining a risk management plan, perform a risk analysis, a risk evaluation, a risk control and finally evaluate the overall residual risk.

Residual risks have been categorized in the following categories: I: unacceptable; II: undesirable; IIIA: less tolerable; IIIB: tolerable and IV: acceptable. Residual risk evaluation is presented in the Investigator's Brochure (IB) and detailed in the Risk Management Report associated with the IB.

Although all risks associated with the intended procedure and device may not be fully known, at this time, the potential risks have been identified through an exhaustive literature search and represent the most up-to-date understanding of risks associated with the proposed therapy.

12.3.1.2 Risk minimization during study start-up

The sponsor will employ the following measures the start-up phase of this investigation:

- The sponsor will select investigational sites that have
  - Sufficient experience in Interventional Neuroradiology, including Endovascular Thrombectomy
  - Sufficient level of clinical expertise and support to manage adverse events that could arise and are able to provide appropriate alternative therapies if required
- The sponsor has clearly defined inclusion and exclusion criteria and will assign monitors to verify compliance to these, to ensure that only appropriate subjects are enrolled
- An extended training will be provided highlighting the differences between (the use of) the Clotild® Smart Guidewire and commercially available guidewires during thrombectomy procedures. Please refer to 18.1.2 Necessary training and experience for more details on the provided training.

12.3.1.3 Risk minimization during the study

The sponsor will employ the following measures throughout the course of this investigation to minimise these risks:

- The investigator will obtain informed consent from each subject or if the subject is incapable of providing consent from the subject's legally authorised representative prior to any study specific assessments being performed.
- The investigator will ensure that every subject undergoes a thorough clinical assessment pre- and post-operatively by trained members of the specialist clinical team. Pre-existing medical conditions will be documented as part of the medical history during the baseline examination to prevent subsequent misinterpretation of clinical information
- The investigator will ensure that the treatment and follow-up of the subjects are consistent with current medical practices and provide the patients with the institutional standard of care in line with expert medical judgment
- The investigator will report all SAEs as per the sponsor/ ethics committee/ regulatory authority defined timelines
- A **Data Safety Monitoring Board** will be set-up:
  - Consisting out of experts in the field. The DSMB will consist out of an uneven number of members, enabling the assessment and conclusion with majority votes. If needed, the DSMB may invite ad hoc team members, such as statistical support. These ad-hoc members will refrain of voting.
  - To review the study safety processes implemented in the study
  - To review safety events happening in the study – for some events, the DSMB may be requesting additional information from the investigational site to allow a comprehensive review.
  - The DSMB will have scheduled meetings after 5, 20, and all subjects have been enrolled in the study.
- Clinical study data will be monitored to ensure the identification, documentation and analysis of all adverse events, compliance with the protocol, adherence to the terms of the participating Ethics Committee to protect the safety and rights of all trial subjects, and compliance with applicable local regulations.
- All Serious Adverse Events will be reported to the Ethics Committees and regulatory agencies according to the local applicable timelines to allow ethical review, and if needed, suspending the study.

12.3.1.4 Rules for temporary enrolment suspension

A Data and Safety Monitoring Board (DSMB) meeting will take place on a regular basis to evaluate the safety of this study and to recommend to continue/discontinue enrolment.

Besides regular DSMB meetings, unscheduled meetings can be organized in case more SAEs and Device Deficiencies occur than expected.

If one of the following events:

- subarachnoid hemorrhage and/or
- symptomatic intracranial hemorrhage

occur, further investigation will be done to assess the severity and the causality to the device if:

- <5 patients are enrolled in the study: each event will be evaluated by the DSMB chairman. The DSMB chairman will give feedback within 48hrs to suspend enrolment to further investigate the event or not.
- ≥5 and <10 patients are enrolled in the study: the study enrolment will be temporarily suspended if >2 events occur since start of enrolment.
- ≥10 and <20 patients are enrolled in the study: the study enrolment will be temporarily suspended if >4 events occur since start of enrolment.

The DSMB will have an urgent meeting to evaluate the events as soon as possible.

A letter summarizing the assessment will be provided to all investigators.

In case the DSMB will assess that it is not safe to continue enrolment in the study, the Investigators, Ethics Committees, Competent Authorities and (if applicable) other local agencies will be informed immediately and actions will be taken to ensure patient's safety is guaranteed.

12.4 Benefit vs Risk Assessment

CSGS will provide physicians with information on the nature of the thrombus which will allow them to make an informed choice on the most effective solution for future mechanical thrombectomy. CSGS is designed to identify the nature of occlusion composition in situ and in real time during the thrombectomy intervention, to provide the physician with unprecedented insights for mechanical thrombectomy as the first-in-line treatment strategy.

In the framework of this pre-market study, information on the occlusion will not be provided to the physicians to aid the decision making on the device to be used and or sequence of devices to be used in thrombectomy. Upon completion of the study, data collected may benefit the future patients at large, through helping physicians to choose the most effective strategy for thrombectomy.

The expected benefits of the CSGS outweigh the potential risks associated with its expected use. Through the CSGS device risk assessment process, a multi-functional team identified risks associated with the design, manufacturing, use of the device and identified the characteristics related to its safety. All clinical risks were considered, including those identified through the Risk Management Documents and through a clinical literature search and review process. The materials and manufacturing processes of CSGS are well characterized and pre-clinical testing allowed for an initial verification of the outcome of the mitigations applied to reduce the associated risks as well as the likelihood of unexpected events.

13 STUDY VISIT ASSESSMENTS

Eligibility will be determined by the investigator based upon review of suitability for inclusion and eligibility criteria.

13.1 INFORMED CONSENT AND REVISION

The Patient Information sheet and Informed Consent Form must receive EC and regulatory approval (if applicable) prior to the initiation of the clinical study. The consent form used at investigational sites must be the approved document identified by its version and date. SENSOME will revise these documents whenever new information becomes available that may be relevant to the subjects. Each time the form is revised, it will be sent to EC and (if appl.) regulatory agencies for approval. When approved, a copy of this information must be provided to the participating subjects in a timely manner by the investigator or his/her authorized designee. The informed consent process described below needs to be repeated each time the form is revised.

13.2 INFORMED CONSENT PROCESS

Prior to conducting any study-related assessments and prior to the use of the study device, the Principal Investigator, or qualified designee, will explain to each Subject or if the patient is incapable of providing consent, the patient's legally authorized representative all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study including, but not limited to, the following: purpose and nature of the study, study procedures, expected study duration, available alternative therapies, and the benefits and risks involved with study participation and the potential treatment. The Principal Investigator, or qualified designee, shall avoid any coercion or undue improper influence on, or inducement of, the Subject to participate and will not waive or appear to waive the subject's legal rights. Subjects will be given a copy of the informed consent form and will be provided ample time to read and understand the document and the opportunity to ask questions. Subjects will be informed of their right to withdraw from the study at any time without prejudice; consent forms will use local non-technical language and be provided in a language understandable to the subject. After this explanation, and before any study-specific procedures have been performed, the Subject and the Principal Investigator, or qualified designee, responsible for conducting the informed consent process will voluntarily sign and personally date the informed consent form. Prior to participation in the study, the Subject will receive a copy of the signed and dated written informed consent and any other written information provided to the subject.

NOTE: In some regions, other individuals then the above-mentioned are entitled to evaluate if it is in the patient's interest to participate in the study and consent on their behalf, if allowed by the local regulations and approved by the (local) Ethics Committee and/or (if applicable) other bodies, and only if the patient is not in the health state to provide informed consent and the legal authorized representative is not present at the time of the consent process. As soon as possible however, the patient or the patient's legal authorized representative must sign the approved informed consent form to confirm study participation and the use of the study data. If, however, several attempts within 7

days to have the Informed Consent Form signed were unsuccessful, the patient's performance outcome data will not be used in the study analysis. Safety data however will be added to the safety analysis.

The Principal Investigator or qualified designee will document in the medical records and/or on the informed consent document the informed consent process, including the date of consent and name of the person conducting the consent process. Documentation of the time of consent is recommended if the informed consent process occurs on the same day as the index procedure.

The patient's eligibility for the study will be assessed by the investigator at a stroke code. If the patient is eligible, the investigator will do their due diligence to explain the study and the associated risks and benefits of participating to the patient and/or their family members. The patient or their family will be encouraged to ask questions regarding the study to aid them in their decision to voluntarily participate in the study. The investigator will allow the participant time to consider their participation and discuss with their family members. The investigator will emphasise to the patient that participation in the study is voluntary. This means they do not have to take part, and that he/she may discontinue their involvement at any time without penalty or loss of benefits to which they are otherwise entitled. If the patient or their family members are unable to make a decision and there is a delay in obtaining informed consent, the investigator will prioritise the care and safety of the patient over the recruitment in the study and as such, patients will not be included. As minimizing the time elapsed between stroke onset and restoration of blood flow is strongly related to improved patient outcome, the investigator will ensure that the patient is offered clot retrieval with commonly used devices.

13.3 Point of Enrolment

Point of enrolment: Patients are considered as enrolled once

1. The patient (or if the patient is incapable of providing consent, once the patient's legally authorized representative) has signed and dated the patient informed consent form as part of the informed consent process (or confirmation of study participation by the individuals mentioned in the NOTE under section: Informed Consent Process).
2. Patient's eligibility has been confirmed at the Investigational Site.
   Some subjects may be referred from other hospitals to undergo an Endovascular Thrombectomy. Prior to the transfer to the Investigational Site, the study patient may receive anti-thrombotic medication to dissolve the thrombus. This may mean that while a patient may be eligible when leaving the referral hospital, she/he no longer meets all eligible criteria at the treating (investigational) center.

13.4 Screen Failures

Patients whose eligibility could not be (re)confirmed at the Investigational Center but for whom a signed and dated Patient Informed Consent Form (see above) was obtained, will be considered as a screen failure.

Only screening assessments will be collected and entered in the eCRF. These patients, however, will be followed up for adverse events till 24hr after obtaining ICF.

13.5 Schedule of Assessments

The investigator is responsible for screening all potential patients and selecting the patients meeting the inclusion/exclusion criteria. As from consent onwards, the patient must be followed for the duration of the study, unless a decision to terminate the patient's participation in the study has been made by the sponsor/ PI and a study termination form is completed. Patients who signed consent and whose eligibility criteria were not confirmed at the treating hospital will be considered screen failures.

The schedule of events is the same for all subjects in the trial. All subjects who are enrolled into the trial will be followed for at least 24 hours (range 16- 36 hrs.) poststudy procedure. Please refer to table 2 for the schedule of the assessments required.

Table 2: Schedule of Assessments

Parameter/Examination	Screening/Baseline	EVT procedure	24H (range 16- 36 hrs.) Post study procedure
Inclusion/Exclusion criteria	X		
Demographics & Medical History incl. Time of stroke onset, NIHSS, GCS	X		
Pregnancy test**	X		
Vital Signs (inc. ECG at screening)	X	X	
Laboratory assessments	X		
Patient Information/ informed consent	X		
Neuro Imaging exams	CT/CTA / MRI/MRA	DSA CT/CTA/MRI/MRA*	CT/CTA/MRI/MRA***
Timings (imaging, tPA, arterial puncture, recanalization)		X	
Thrombus collection		X	
AE/SAE		X	X
Concomitant medication, incl. Anti-thrombotic treatments	X	X	X

* if available per local hospital practice

** according to site specific standard of care (e.g. test, verbal communication)

*** CT/CTA / MRI/MRA if available per local hospital practice (range 2hrs - 36hs post procedure)

13.6 SCREENING/BASELINE VISIT

The following pre-procedure data must be collected before enrolment for all subjects:

- Confirmation that all inclusion and none of the exclusion criteria have been met
- Informed consent
- Demographics (Year of Birth, gender, height, weight, race*)
- Medical history (incl. NIHSS, GCS and mRS) and time of stroke onset
- Pregnancy test according to site specific standard of care (e.g. test, verbal communication)
- Vital Signs (Blood pressure, pulse, ECG (screening only)
- Concomitant medications, including Anti-thrombotic treatments that have been started prior to study participation.
- Laboratory assessments: if lab assessment is not collected at screening as per normal hospital practice, the first available assessment result will be provided.
    - Hematology: red blood cell count, white blood cell count, hemoglobin, hematocrit, platelets
    - Chemistry: Natrium, Potassium, Calcium
    - Coagulation: APTT, PT, INR, fibrinogen
    - Liver function tests: ALT, AST, GGT, total alkaline phosphatase, total bilirubin, BUN, albumin
    - Kidney tests: Creatinine
    - Lipids : cholesterol, HDL-cholesterol and LDL-cholesterol, triglycerides
    - Infection parameters: CRP
- Neurological examination (Computed Tomography (CT) scan/CT angiography or MRI/MR angiography), including images that have been taken prior to study participation.

Subject's evaluation will be performed in accordance with the standard of care at the participating sites in order to establish the diagnosis of acute ischemic stroke eligible for EVT.

*race: Intracranial atherosclerotic disease (ICAD) is an important root cause of ischemic stroke. Race of study patients will be collected as the incidence of ICAD is not equally divided amongst all races.

13.7 EVT PROCEDURE

Subjects will undergo the EVT procedure in accordance with standard of care. No specific study requirements, besides the ones mentioned here below will be asked.

Timings of the different steps will be recorded, such as:

- Time of patient arrival in treating hospital,
- Time of tPA start, if applicable
- Time of anaesthesia start, if applicable
- Time of skin puncture
- Time of angiogram, confirming patient's eligibility

- Time of thrombus removal
- Time of skin closure

A worksheet may be used to enter the above mentioned in formation. Worksheets will be considered source documents.

13.8 STUDY PROCEDURE

Clotild® guidewire will be inserted and up to 6 measurements will be done: 1 measurement distal to the access catheter in circulating blood (this is the reference measurement), 1 measurement proximal to the site of occlusion, 2 to 3 measurements inside the occlusion and 1 measurement at the most distal advancement of the guidewire (ideally distal to the occlusion). Each of these measurements will be tagged using the tablet interface.

Note that the study procedure includes the manipulation of the CSGS, from the tablet preparation to removal of the study device form the sheath, and not the clot removal.

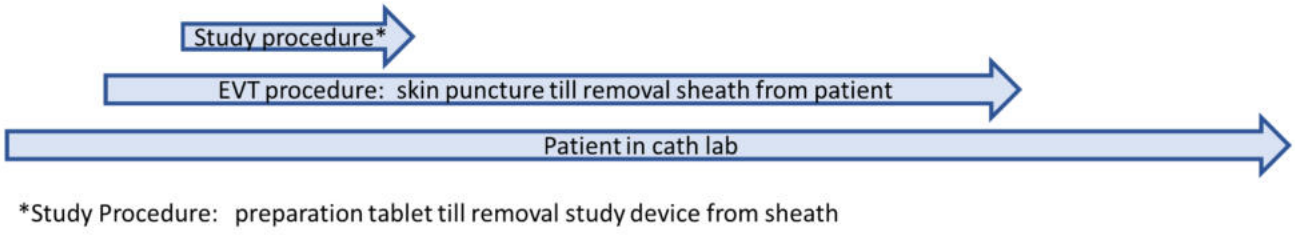

Figure 7: Schematic explaining how the study procedure is structured within the EVT.

During the study procedure the CSGS may be used to navigate other devices involved in the EVT, taking the CSGS IFU into consideration.

Procedural success is defined as the ability to navigate CSGS to the occlusion site and measure electrophysiological properties of the occlusion.

A Treated patient is a patient in whom the CSGS went through the introduction sheath.

The occlusion material recovered during the EVT procedure will be immediately stored in a preservative solution of formaldehyde (refer to section 14.1) and sent to the histo-pathology lab for preparation. Analysis of histo-pathology of the occlusion will be conducted in a core central laboratory. Correlation with the electrophysiological properties will be done by the SENSOME data team.

During the procedure, the following data will be collected:

- Digital Subtraction Angiography images
- Vascular perforation, dissection, or device failure.

- Vital Signs (Blood pressure, pulse)
- Concomitant medication, including Anti-thrombotic treatments
- All AEs and SAEs

At the end of the procedure, the following activities will be completed:

- Collection of the occlusion material (or piece of occlusion), which will then to be sent to the Core Lab (refer to 'Histopathological clinical protocol description per section 14.1).
- Collection of the CSGS, which will then be sent to SENSOME for physical inspection.
- CT/CTA / MRI/MRA if available per local hospital practice will be sent to an independent Core Lab for angiographic evaluation.

The sponsor's Clinical Field Specialist will be present during the procedure to observe the use of the device and provide the site with support.

Timings of the different steps will be recorded, such as:

- Time of insertion CSGS in the catheter sheath introducer
- Time of electrophysiological parameter collection
- Time of removal CSGS from the catheter sheath introducer

A worksheet may be used to enter the above mentioned information. Worksheets will be considered source documents.

13.9 24 HOURS (RANGE 16-36HRS) POST-PROCEDURE

Subjects will undergo standard of care assessment post EVT procedure according to the current practice of the hospital.

The following data will be collected:

- CT/CTA / MRI/MRA if available per local hospital practice (range 2hrs - 36hs post procedure)
- Concomitant medications, including Anti-thrombotic treatments
- Adverse events and Serious Adverse events

For all subjects that decease prior to the 24H (range 16-36hrs) assessment, available information regarding the primary cause of death and date/time of death will be recorded.

13.10 MANAGEMENT OF PATIENTS AT THE END OF THE STUDY

Patient management beyond the participation in this study should be according to the standard of care of the investigational site and/or treating physician.

14 STUDY HANDLING PROCEDURES

14.1 HISTOPATHOLOGICAL CLINICAL PROTOCOL

The following instructions will be provided to the site, for shipment of the Retrieved clots to the Core Laboratory:

- In the procedure room, set the clot into Formol solution (Formaldehyde 4% = 10% formalin solution). As an example, reference VWR FOR0020AF59001 can be used but any other solution of similar composition will be acceptable.
- Identify the clot with the subject study number.
- Send the clot to the pathology lab for paraffin embedding. Clots needs to be in the formol solution for at least 24h before paraffin embedding.
- Send paraffin embedded clots to the Core Histology Laboratory.

An operation manual will provide detailed information on the handling and processing of the clots.

14.2 RETURN OF USED CLOTILD® SMART GUIDEWIRE TO SPONSOR

- Used Clotild® Smart Guidewires will be washed with sterile saline, rolled up and stored in a biohazard plastic bag (provided by the sponsor) with device number indicated.
- Up to 5 devices will be stored before shipment to SENSOME for physical inspection.

An operation manual will provide detailed information on the handling and processing of the used devices which will also be summarized in section 8.

15 STATISTICAL CONSIDERATION

15.1 STATISTICAL ANALYSES

Sponsor may assign a third party to be responsible for statistical analyses.

A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections.

Additional details will be provided in the Statistical Analysis Plan.

Given the fact that this is a single arm clinical trial no statistical comparisons will be performed. For the primary safety endpoint, statistical analysis will consist only of descriptive analysis. For performance endpoints, statistical analyses will consist of descriptive analysis of prediction performance estimators and correlation analyses with statistical modelling.

15.2 ANALYSES POPULATION

This study will be conducted in subjects presenting an acute ischemic stroke due to M1 occlusion, eligible for EVT based on neuro-interventionist and/or neurologist investigators' opinion.

Intention To Treat (ITT) Population

All patients who were enrolled, so all patients (or legally authorized representatives) who signed and dated the patient information consent form even though the CSGS was not used in the subject.

The **safety analysis** (amount of AE) will be performed on the intention to treat (ITT) population.

Treated Population

All patients in which the guidewire went through the sheath, even though if not all eligibility criteria were met or if a device failure occurred or if the clot could not be retrieved.

The **primary safety endpoint** will be determined on the Treated Population.

Per-protocol Population

All patients from the Treated Population who comply to all eligibility criteria.

No separate analyses will be performed for the per-protocol population.

Development Performance Population

This population includes patients from whom at least 1 evaluable acquisition was captured by the CSGS. An evaluable acquisition is defined as a "CLOT tag" or "Clot or beyond" tag with non-anomalous (see criteria section 15.6) impedance measurement. Data of this population will be used during the development phase to build the different models for classification of RBC-positive and platelet-positive.

Local-Scale Performance Population

This population includes patients for whom non-anomalous acquisition was collected by the CSGS during at least one tagged measurement with clot contact excluding patients from the Development Performance Population. Data of this population will be used during the validation phase to validate the model built during the development phase.

The analysis of the **primary performance endpoint** will be performed on data from the Local-Scale Performance Population.

Clot-Scale Performance Population

All patients from the Local-Scale Performance Population of which the clot could be retrieved for histological assessment.

Performance evaluation of the secondary performance endpoints related to the clot scale will be done on the Clot-Scale Performance Population.

15.3 DEVELOPMENT PHASE AND VALIDATION PHASE OF CSGS PREDICTION MODEL

A major objective of this study is to evaluate the prediction model(s) of the Clotild® Smart Guidewire System. These prediction models are based on physical properties of the impedance measurements captured by the sensor, complemented with a comparison to suitable labels for each endpoint (a.k.a. phenomenological modelling). The impedance dataset that will be constructed during the clinical investigation should serve to develop the prediction models (model development) and to evaluate their prediction accuracy (model evaluation). Such an evaluation methodology is inspired from *Good Machine Learning Practice for Medical Device*[1] and avoids any optimistic bias.

To this end, the study is split in two phases:

- **the development phase**, where model optimization is being made to arrive at a single prediction model per endpoint developed on the full development dataset.
- **the validation phase**, that is solely used to assess the generalization performance of the model(s) developed during the development phase.

In order to develop the prediction model(s), data from the development dataset are analysed on an ongoing basis.

When moving to the validation phase the model(s) shall be locked, remaining unchanged during the course of the validation phase.

This procedure of splitting the dataset into two independent datasets will be performed for the primary performance endpoint assessment as well as for the secondary and tertiary endpoint assessments where prediction is done.

15.4 ENDPOINT ANALYSIS

15.4.1 Primary Endpoint analysis

For the **Primary Safety Endpoint** descriptive statistics will be provided showing the proportion of patients with intracranial vessel perforation and / or dissection due to Clotild® usage. Furthermore, a 95% confidence interval will be estimated. The primary safety endpoint will be determined in all patients in whom the guidewire went through the introduction sheath.

The **Primary Performance Endpoint** is defined as the ability to perform binary classification of individual electrophysiological parameter measurements (local scale) by distinguishing local regions with substantial red blood cell content (RBC-positive) from regions with negligible red blood cell

[1] *Good Machine Learning Practice for Medical Device Development: Guiding Principles (FDA, October 2021)*

content (RBC-negative) in the occlusion. This endpoint can be understood as the ability for an automated system to rank individual electrophysiological measurements in the occlusion according to the local scale content of RBC (the predicted RBC-content score). Evaluation is based on expert labelling of individual electrophysiological measurements as a binary outcome: RBC-positive (region with substantial RBC content) and RBC-negative (region with negligible RBC content). This labelling, considered as ground truth, is made by (at least) two independent SENSOME experts that cumulate the relevant experience in electrochemical impedance measurements of different biological tissues from previous non-clinical research.

- The performance of the CSGS model will be assessed by the performance metric Area Under the Receiver Operator Characteristic curve (AUC of ROC) computed from the RBC-content score predicted on the validation dataset only.
- The ROC curve will be defined by the sensitivity (true positive rate) on the Y-axis and 1-specificity (false positive rate) on the X-axis. The ground truth is defined as the binary classification of the local regions into RBC-positive or RBC-negative content performed by SENSOME experts.
- The comparator will be the binary classification score determined by the CSGS model. The CSGS model will be developed using interventions from the development phase (Development Performance Population) while it will be validated on the impedance data from the validation phase (Local-Scale Performance Population).

15.4.2 Secondary Endpoint analysis

There are 7 secondary endpoints. Impedance data from the interventions in the development and validation datasets will be the same as for the primary performance endpoint.

1. The concordance between aggregated occlusion measurements (clot scale) done by CSGS, and the histopathology results of the clot retrieved during the EVT procedure, regarding red blood cell content in the occlusion.
   - To determine the histopathological results of the clot, the RBC composition (value between 0 and 1) will be averaged over the 3 analyzed slides provided by the Core Laboratory.
   - Significant correlation will be judged at the 0.05 significance level by the t-statistic of the relation between RBC content as output by the prediction model and the RBC content as quantified by the MSB-staining histological analysis.
2. The ability of CSGS detecting the proximal end of the occlusion (sensor-scale), as compared to the physician's labelling (tag 'PRE-CLOT' for no occlusion contact and tag 'CLOT' for occlusion contact). The concordance will be judged by the Area Under the Receiver Operator Characteristic curve on the validation dataset. Evaluation will include those interventions from the validation set where the `PRE-CLOT' and `CLOT' tagged measurements were acquired with

at most one missing or anomalous individual measurement (see identification of anomalous measurements in 15.6).

3. Procedural success defined as the ability to navigate CSGS to the occlusion and measure electrophysiological properties of the occlusion. Procedural success is achieved from the moment that at least 1 evaluable measurement is captured by the CSGS.
4. The ability to perform binary classification of individual electrophysiological parameter measurements (local scale) by distinguishing local regions with substantial platelet content (platelet-positive) from regions with negligible platelet content (platelet-negative) in the occlusion.
   - The ability to perform binary classification will be evaluated by the performance metric Area Under the Receiver Operator Characteristic curve (AUC of ROC) computed from the platelet-content score predicted on the validation dataset. The same methodology will be used as for the primary performance endpoint.
5. The concordance between aggregated occlusion measurements (clot scale) done by CSGS, and the histopathology results of the clot retrieved during the EVT procedure, regarding platelet content in the occlusion.
   - To determine the histopathological results of the clot, the platelet composition (value between 0 and 1) will be averaged over the 3 analyzed slides provided by the Core Laboratory.
   - Significant correlation will be judged at the 0.05 significance level by the t-statistic of the relation between platelet content as output by the prediction model and the platelet as quantified by the CD42b immunochemistry staining histological analysis.
6. The ability to perform binary classification of individual electrophysiological parameter measurements (local scale) by distinguishing local regions with substantial fibrin content (fibrin-positive) from regions with negligible fibrin content (fibrin-negative) in the occlusion.
   - The ability to perform binary classification will be evaluated by the performance metric AUC of ROC computed from the fibrin-content score predicted on the validation dataset. The same methodology will be used as for the primary performance endpoint.
7. The concordance between aggregated occlusion measurements (clot scale) done by CSGS, and the histopathology results of the clot retrieved during the EVT procedure, regarding fibrin content in the occlusion.
   - To determine the histopathological results of the clot, the fibrin composition (value between 0 and 1) will be averaged over the 3 analyzed slides provided by the Core Laboratory.
   - Significant correlation will be judged at the 0.05 significance level by the t-statistic of the relation between fibrin content as output by the prediction model and the fibrin content as quantified by the MSB-staining histological analysis.

15.4.3 Tertiary Endpoint analysis

There are 6 tertiary endpoints. Impedance data from the interventions in the development and validation datasets will be the same as for the primary performance endpoint. These endpoints are

more exploratory by assessing the correlation between the CSGS measurements with intervention parameters such as:

1. The arterial wall detection for individual measurement, specifically the local detection of arterial wall vs. clot when clot-contact is ensured.
2. The ability of CSGS detecting the distal end of the occlusion.
3. The ability of CSGS predicting the number of thrombectomy passes.
4. The ability of CSGS predicting the first pass effect (patients in whom the clot was removed on the first pass with a TICI score of 2c or 3).
5. The ability of CSGS predicting the etiology of the clot.
6. The ability of CSGS predicting the type of device(s) with better chances to remove the clot.

15.5 STUDY SAMPLE SIZE CALCULATIONS

The sample size calculation is driven by the number of patients needed in the development and validation datasets. The size of the development dataset is justified by the minimal number needed to achieve a target prediction performance for the primary performance endpoint. The size of the validation dataset is justified by the minimal number needed to achieve a sufficiently precise estimate of the primary performance endpoint around the target performance, as computed by the width of the confidence interval.

The sample size calculation is thus split in two parts, one for the development set and one for the validation set.

Development set size

The development set size was fixed to obtain a reasonable performance concerning the primary performance endpoint, based on preliminary research performed by SENSOME on an ex-vivo dataset (*DND_tr-0033-clot-composition-phenomenological-model-development_v1*). The standard approach at Sensome was to use machine learning techniques to cope with the complexity of the signal. However, our accumulated experience guided the design of a phenomenological model (based on observations and on physical properties of the signal). Its performance on local-scale composition prediction, evaluated on the ex-vivo dataset, is comparable to the machine learning model performance previously developed. The fine-tuning of its parameters has got only a minor influence on the performance, as assessed on the ex-vivo dataset.

Its extrapolation for thrombectomy-like procedures requires an additional rule to distinguish the arterial wall and potentially a fine-tuning of one of its parameters. Overall the number of examples needed to complete the first local-scale clot composition prediction model is constrained by the observation of ideal cases (locally pure RBC content and locally pure platelets content). Based on the

fraction of pure cases that was observed on the ex-vivo data set, and on rules to sub-sample this data set regarding the number of clot contact measurements per intervention, we find that N = 11 is an adequate estimate of the development sample size.

We thus require a number of **N_D = 11 interventions** with at least 1 evaluable measurement to be included in the development set to reach near optimal performance with respect to primary performance endpoint assessment (Development Performance Population).

Validation set size

The minimum number of **N_V** interventions to be included in the validation dataset to estimate the performance Â with sufficient statistical confidence margin is determined, with Â the area under the ROC curve (AUC) of the prediction model obtained on the validation sample of the population.

The following assumptions are made:

- **Estimated average number of independent individual measurements from a single tagged acquisition with clot contact = 5.44** (based on the quality check of data collected in the first 9 procedural successes)
- **Estimated average number of tagged acquisitions with clot contact per intervention = 3** (based on the quality check of data collected in the first 9 procedural successes)
- **Estimated number of RBC-positive cases = 53%** (based on the quality check of data collected in the first 9 procedural successes)
- **Expected number of RBC-negative cases = 47%**
- **An AUC of 0.85 is assumed with a maximal width of 0.1 for the 95% confidence interval**

With these assumptions, using the Hanley and McNeil estimate (Hanley and McNeil 1982) for the confidence interval to reach an expected AUC of 0.85 and a maximal width of the 95% confidence interval of 0.1, a number of **N_V = 14 interventions** with at least 1 evaluable measurement valid interventions are necessary for the validation set (Local-Scale Performance Population).

Total sample size

The total sample size has to be corrected for a 40% anomaly rate (see section 15.6).

The **total sample size** $N = (N_D + N_V)/0.60 =$ **42**.

15.6 MISSING DATA

To assess the possible impact of missing data on the primary safety endpoint a sensitivity analysis will be conducted. Given the primary safety variable is a binary variable it is rather straightforward to assess the impact of different assumptions. In a worst case scenario all missing data are considered failures which will lead to the worst case scenario estimator of the proportion of perforations/dissections.

Regarding the impedance measurements captured by the CSGS, data might be missing or anomalous, having an impact on the performance endpoints. Based on the Device Deficiency rate obtained in the first 31 treated subjects, the estimated amount is 40%. This missingness/anomaly might be due to the following reasons:

- Technical malfunctions, leading to missing data or anomalous data, among which:
  - device anomaly caused by manufacturing anomaly
  - device anomaly due to electrical connection loss during navigation
- Use error, leading to:
  - missing data because measurements have not been tagged
  - anomalous data because the sensor was covered by the microcatheter while the measurement was tagged, as confirmed by the Imaging Core Lab on the angiography images corresponding to the tagged measurement.

The criteria to discard anomalous measurements due to technical malfunction include:

- Any acquisition associated with an error code raised by transmitter software (for instance due to loss of communication between sensor and transmitter) will be excluded from the development and validation datasets.
- Electrophysiological measurement from an electrode pair that shows a constant raw digital signal across acquisition frequencies (constant or piecewise constant with a single step) is considered anomalous and will be excluded.
- Electrophysiological measurement from an electrode pair that shows digital saturation consistently from REFERENCE to PRE-CLOT is considered anomalous; all remaining measurements made with this electrode pair will be excluded from the datasets.
- Anomalies related to invalid reference measurements are reported as too-high dispersion across electrode pairs in the `REFERENCE' measurement. Persistence of the anomaly up to the `PRE CLOT' measurement requires exclusion of all measurements from the concerned electrode pairs.

To deal with missing CSGS data, an attrition rate was taken into account in the sample size calculation. Technical malfunctions rate will be reported in the final Clinical Study Report.

Clinical experience reports that roughly 40% of clots cannot be retrieved during the procedure. This will lead to a smaller sample size for the evaluation of secondary endpoints related to the concordance between occlusion measurement done by CSGS, and the histopathology results of the clot retrieved during the EVT procedure. Missing histopathological data will not be replaced or imputed and the analysis will only be performed on the available data. However, over the first 31 treated subjects, 30 clots were collected and analyzed by the histology corelab, which is better than expected and decreases the impact of this potential missing data.

15.7 BIAS

To minimize bias, an independent Data Safety Monitoring Board (DSMB) (see section 20.3) will be responsible for monitoring safety and performance aspects of the study. The DSMB consists out of an uneven number of experts in the field, enabling the assessment and conclusion with majority votes. If needed, the DSMB may invite ad hoc team members, such as statistical support. These ad-hoc members will refrain of voting. To review safety events happening in the study – for some events, the DSMB may be requesting additional information from the investigational site or the core lab to allow a comprehensive review. DSMB will be responsible of adjudicating the primary safety endpoint.

Secondly, to evaluate the Primary Performance Endpoint a binary classification of individual electrophysiological parameter measurements into `RBC-positive' and `RBC-negative' is performed by 2 SENSOME experts independently. In case of discrepancies, a 3rd expert will decide on the classification. This process cannot be performed by independent reviewers. Following SENSOME's internal procedure (SEN_QAS_SOP_1010), experts involved in annotating data shall not inspect the incoming validation dataset before the development is declared finished (the prediction models being fixed). As dataset inspection is also routine to detect anomalies, another SENSOME expert not involved in the development could be designated in the transition period (when the development phase is not terminated but the development set is completed).

Thirdly, an expert in the field of histopathology from an independent Core Lab (Mayo Clinic) will perform the histopathological analysis of the clots. The core lab will be blinded for the results of the CSGS. Rules of operation and responsibilities are outlined in the Core Lab Instructions.

Fourthly, another independent core lab (UCLA) will check the images. The imaging Core Lab will be set-up by 2 experienced readers. Both will check independently the pre-procedural, procedural and post-procedural images. Both readers will assess the primary safety endpoint. In case of disagreement between the 2 readers, a decision will be made by consensus. Rules of operation and responsibilities are outlined in the Core Lab Instructions.

It is well known that some clots might not be available for histological assessment (clot retrieval not successful and/or impossibility to collect the clot fragments after EVT). Next to that data captured by the CSGS can be anomalous/missing. So the measures of agreement will only be based on those clots or on data from the CSGS that are available. The possible bias introduced by this restriction cannot be

assessed. It will be assumed that the performance of the medical device is not impacted by this selection bias.

Clinical study data will be monitored to verify its accuracy. Data Management will send out queries to the site in case of inconsistencies, contradictions, suspicious values or missing data.

16 STUDY CONDUCT AND MANAGEMENT

16.1 ETHICAL CONSIDERATIONS AND REGULATORY APPROVAL

The study will be carried out in accordance with the Declaration of Helsinki and Good Clinical Practice (ISO 14155:2020) and laws and regulations applicable to the country, where the study will be performed.

16.2 AMENDMENTS

The dataset that will be constructed during this clinical investigation should serve to train statistical learning models. Besides this study, SENSOME has other projects providing input to this learning model. Information obtained from these other projects (thus increasing understanding) may trigger the need to amend this Clinical Investigation Plan.

This Clinical Investigation Plan shall thus be amended as needed throughout the clinical investigation in accordance with written procedures for the control of documents and document changes. Each amended document will have a new version date and version number.

An overview of the previous versions will be listed. Documentation of changes can be found in annex 1 and shall include a description of the changes and justification of the changes.

The amendments to the CIP and the subject's informed consent form shall be notified to, or approved by, the EC and regulatory authorities.

If the amendment impacts the integrity of the clinical investigation, the data collected before and after the amendment shall be analysed statistically to assess the effect of the amendment on performance, effectiveness or safety analysis. This analysis shall be included in the clinical investigation report.

16.3 DATA MANAGEMENT

A validated eCRF (Viedoc) will be used to collect clinical data for this study. The Investigator and site staff will be trained on and have restricted access to the eCRF to enter the data. An explanation for the omission of any required data should appear on the appropriate eCRF page or other data collection forms. The data as entered in the eCRF by the Investigator will be stored in the EDC system.

The eCRF will contain a record of the subject's eligibility to enter the study, relevant medical history, pre-procedure assessments, concomitant medications, a record of all investigational products used

during the procedure, all procedural complications and adverse events, as well as discharge, follow up, and any unscheduled visits.

The investigator must sign and date the specified section of the eCRF to confirm that she/he has reviewed the data and that the data are complete and accurate.

Data validation will be performed. The Investigator is responsible for complete and correct data and should respond to queries within agreed timelines (data entry on the eCRFs within 5 days following subject enrolment). CRF completion guidelines will be provided. Further details on the data management procedures are documented in the Data Management Plan.

After database lock, data from the Clot-Out study database will be transferred to SENSOME in a pre-agreed format. SENSOME will provide digital copies of the subject data per site to the Investigator for on-site storage. All original source documentation is expected to be stored at the site for the longest possible time as required by local applicable regulations or as specified in the contract, whichever is longer. The records must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived following the study conclusion, according to local regulations or as specified in the contract, whichever is longer.

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national regulations. Essential documents include:

- EC approvals for the study protocol and all amendments
- All source documents
- eCRF contents
- Evidence of Patient Information Letters that have been sent to the patients; Patients signed ICFs (if required with study number and title) or Patient Information Letters where refusal of participation has been indicated
- Any other pertinent study document.

SENSOME will notify the investigators/institutions when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify SENSOME.

After the study has been completed and locked, the study data will be deleted from the servers from Viedoc on request of SENSOME.

16.4 USABILITY

As part of the requirements to submit the technical file to the Notified body for Conformity assessment, a summary of the device's usability needs to be provided. This summary will give more insight in identification of use errors that could lead to safety issues of the device. The usability

questions will be part of the Case Report Form and will have to be completed immediately after the procedure by completing a questionnaire on the medical tablet.

16.5 SOURCE DOCUMENT REQUIREMENTS

A source document is described in ISO 14155:2020 as "All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation." Source documents may be the Medical records, consultant letters, worksheets, etc. The investigator will clearly mark clinical records to indicate that the subject is enrolled in the study.

Usability questions (see above) will be completed directly on the medical tablet. Tablet information will not be recorded in the medical file and will be considered as source documents.

16.6 PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the Principal Investigator or site personnel did not conduct the study according to the Clinical Investigation Plan.

Deviations are only allowed to protect the life or physical well-being of a subject in an emergency. When unforeseen circumstances occur that are beyond the Investigator's control, (e.g. subject did not attend scheduled follow-up visit) the event is still considered a deviation.

Deviations shall be reported to the sponsor regardless of whether or not they are medically justifiable or taken to protect the subject in an emergency. Subject specific deviations will be reported on a CRF. Non subject specific deviations will be reported to the sponsor in writing. Investigators will also adhere to procedures for reporting study deviations to the Ethics Committee in accordance with their specific reporting policies and procedures.

Except under emergency circumstances, the investigator is not allowed to deviate from the protocol. Deviations to the investigational plan, that are decided by the investigators, to protect the rights, safety and well-being of patients shall be documented and reported to the sponsor, as soon as possible.

No deviations from the protocol are permitted except under emergency circumstances to preserve the rights, safety and or well-being of a trial subject; in particular, it is recommended to make every effort to avoid deviations from the protocol including, but not limited, the following:

- Inclusion of a patient that does not meet the inclusion criteria
- Inclusion of a patient that meets any of the exclusion criteria
- Missing any data related to the primary and secondary objectives
- Procedures not conducted as prescribed according to the randomization arm, if relevant
- Patient and/or assessor of study clinical endpoints becoming unblinded to the patient's randomization assignment, if relevant

- Follow-up being performed outside the protocol specified visit window

16.7 EARLY DISCONTINUATION OF SUBJECTS

All Subjects have the right to withdraw from participation at any point during the study and without prejudice of further treatment. Site staff should obtain written documentation from the Subject that wishes to withdraw his/her consent for future follow-up visits and contact. If site staff are unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record. In addition, the appropriate eCRFs must be completed for the Subject and clear documentation of the subject's withdrawal must be provided to the Sponsor.

In addition, Principal Investigators also have the ability to terminate subject participation in the study. A description of the reason for a subject's termination will be documented in the subject's medical records. Reasons for termination can include: study completion, Subject withdrawal, physician-directed Subject withdrawal or death.

16.8 STUDY TERMINATION

The sponsor reserves the right to discontinue the study at any time for any reason. The sponsor may also discontinue the study at a site for poor performance or compliance. If warranted, the study may be suspended or discontinued early for any of the following reasons:

- It becomes apparent that subject enrolment is unsatisfactory with respect to quality or quantity
- Data recording is inaccurate and/or incomplete
- Violations or deviations from the signed protocol
- The incidence and/or severity of adverse events in this study indicate a potential health hazard caused by the device under study.

The investigator must implement the Sponsor's request to terminate the study in a time frame that fits with the subject's best interest. In case of early termination of the clinical investigation all Ethics Committees and Competent Authorities will be promptly informed by SENSOME with a report of the reasons of the early termination.

16.9 CONSEQUENCES OF SITE OR STUDY DISCONTINUATION

In case of early investigational site/study/patient suspension or termination, the patient will be followed according to the standard of care. This decision will be documented, and the investigator will be informed of this decision. For all patients, a study termination form will be completed. The patient's data will be collected and statistically analyses according to the data-management plan defined previously.

17 SAFETY MANAGEMENT

17.1 DEFINITIONS

These definitions are aligned with ISO14155:2020 standard and the MDR 2017/745.

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons whether or not related to the investigational medical device and whether anticipated or unanticipated. 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 investigational medical devices.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons that either resulted in : • a life-threatening illness or injury, or • a permanent impairment of a body structure or a body function including chronic diseases, or • in-patient or prolonged hospitalization, or • medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment. NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. 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.
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, and inadequacy in the information supplied by the manufacturer. Some study specific device deficiencies will be defined by the DSMB for assessment in the DSMB's scheduled meetings. These device deficiencies will be listed in the DSMB charter.
Use error	User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. NOTE 1: Use error includes the inability of the user to complete the task NOTE 2: Use errors can result from mismatch between the characteristics of the user, user interface task or use environment NOTE 3: Users might be aware or unaware that a use error has occurred NOTE 4: An unexpected physiological response of the subject is not by itself considered a use error. NOTE 5: A malfunction of a medical device that causes an unexpected result is not considered a use error
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

17.2 EVENT SEVERITY

Event severity is classified as follows:

Mild: awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae

Moderate: interferes with the patient's usual activity and/or requires symptomatic treatment

Severe: symptom(s) causing severe discomfort and significant impact on the patient's usual activity and requires treatment.

17.3 CAUSALITY/RELATIONSHIP

The investigator will assess the causality of all adverse events in relation to the research, i.e., the relationship between the AE / SAE and:

- the investigational device
- the study procedure
- the EVT procedure, excluding study procedure.

Note that the study procedure includes the manipulation of the CSGS, from the tablet preparation to removal study device form the sheath, and not the clot removal.

Each Adverse Event will be classified according to four different levels of causality:

Not related:
The relationship to the study device or study procedure or EVT procedure can be excluded when:

- the event has no temporal relationship with the use of the investigational device, or the study procedures related to application of the investigational device;
- the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact the event;
- the event involves a body-site or an organ that cannot be affected by the device or study procedure; - the event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable.

Possible:
The relationship to the use of the investigational device or to the study procedure or to the EVT procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Probable:
The relationship to the use of the investigational device or to the study procedure or to the EVT procedure seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship:

The event is associated with the use of the investigational device or to the study procedure or to the EVT procedure beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that:
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the SAE follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the SAE (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of study device/study procedures and the Adverse Event.

An Adverse Event can be related to the investigational device and to the study procedure and to the EVT procedure (study procedure excluded).

17.4 Adverse Event Reporting

Adverse Events

All Adverse Events are to be reported via the eCRF within 5 business days of the event.
The description of the AE will include the date and time of onset, seriousness, relationship to the device or procedure, the results of any diagnostic procedures or laboratory tests, any treatment recommended, and the outcome of the event. In the circumstance that an AE has not resolved by the time of the subject's completion of the trial, an explanation will be entered on the appropriate CRF.

Serious Adverse Events

The investigator must report to sponsor details of any SAEs occurring during the study within 24 hours of awareness of an event via the Adverse Event (electronic) Case Report Form in the study's electronic database, as that will trigger an immediate e-notification to the Sponsor and its designee. The site must provide additional information, if required by the sponsor or designee.

If the electronic data capture (EDC) system is unavailable, a written report by e-mail to the sponsor and its designee will be acceptable.

In the event of subject death every effort should be made to obtain a copy of the autopsy report and/or death summary. Information on the cause of death and its relationship to the study device will be determined by the Principal Investigator and recorded on the appropriate CRF. Copies of an autopsy report, if available, and/or a death summary must be included with this CRF form.

The Data Safety Monitoring Board (DSMB) will review all AE/SAE, as per the DSMB Charter, throughout the study. Adverse Events of special attention need to be reported to the DSMB or DMSB chairman without delay.

17.5 Reporting of adverse events to Ethics Committees and regulatory authorities

All device deficiencies and events related or not to the study device or the study procedure or to the EVT procedure (study procedure excluded) must be recorded by the Investigators in the EDC system.

The Principal Investigator will inform the Ethics Committee of any Serious Adverse Events and any other events as per local Ethics and / or regulatory authority's requirements.

Regarding the reporting from SENSOME to the Regulatory authorities, the following events are considered reportable events in accordance with Chapter VI, article 80 and Annex XV of the MDR 2017/744:
a. any SAE, that has a causal relationship with the investigational device or the investigation procedure or where such causal relationship is reasonably possible. Only "not related" events are excluded from reporting. If either the sponsor or the investigator has assigned a higher causality level than "not related", the event should be reported.
b. any DD, that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
c. any new findings in relation to any event referred to in points a) and b).

Once EUDAMED is available and fully functional the obligations and requirements that relate to performing safety reporting via EUDAMED shall apply from the date corresponding to six months after the date of publication of the notice referred to in Article 34(3) (Functionality of the EUDAMED) of the MDR.

The sponsor shall fully record all of the following:

a) Any adverse event of a type identified in the clinical investigation plan as being critical to the evaluation of the results of that clinical investigation;
b) Any serious adverse event;
c) Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
d) Any new findings in relation to any event referred to in points (a) to (c).

Reporting must be performed:

a) For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: **immediately (but not later than 2 calendar days)** after awareness by SENSOME of a new reportable event or of new information in relation with an already reported event. This includes events that are of significant and unexpected nature such that the become alarming as a potential public health hazard or serious health threat. It also includes the possibility of multiple deaths occurring at short intervals.
b) For any other reportable event or a new finding/update to a reportable event**: immediately (but not later than 7 calendar days)** following the date of awareness by SENSOME of the new reportable event or of new information in relation with an already reported event.

The reportable events occurring in Third Countries[2] in which a clinical investigation is performed under the same clinical investigation plan have to be reported in accordance with this section to the National Competent Authorities (NCA) of the European countries in which the clinical investigation is being conducted.

- The NCA shall start receiving the reportable events occurring in Third Countries as soon as the clinical investigation is authorized to start in that Member State.
- Events occurring in Third Countries after the participating European sites have closed shall continue to be reported.

17.6 DEVICE DEFICIENCIES REPORTING

All study device deficiencies are to be reported via the e-CRF.

Device malfunctions and use errors should be reported without unjustified delay (within 24 hours) via the e-CRF. If the electronic data capture (EDC) system is unavailable, a written report by e-mail to the sponsor and its designee will be acceptable. In the case of a device deficiency or malfunction, the study device must be returned to the sponsor for analysis.

Device malfunctions not involving study subjects are to be reported to the sponsor via email.

Device deficiencies needing specific follow up as defined by the DSMB will be reported to the DSMB for further assessment.

17.7 REPORTING OF EVENTS / DEFICIENCIES RELATED TO ANCILLARY DEVICES

Non-study device deficiencies occurring in study patients will need to be reported by the investigator to the manufacturer of these devices. However, related adverse events are to be reported in the eCRF.

[2] Countries other than Switzerland, Turkey and those belonging to the EEA.

17.8 Safety Analysis

The DSMB will have scheduled meetings at regular times to assess the safety in the study. A detailed DSMB charter approved by the DSMB members will clarify the methodology used by the board.

Once all patients have been enrolled and completed the study, a detailed Safety Analysis will be done.

All adverse events will be listed and categorized according to severity, seriousness and causality to the study device or the study procedure or to the EVT procedure (study procedure excluded).

Device Deficiencies will be categorized in malfunctions, use error, and inadequacy in the information supplied by the manufacturer and those associated with adverse events and those that may have led to a life-threatening situation if no action was taken.

Trends will be identified, and conclusion will be made in a report.

The Safety Analysis Report will be shared with the Data Safety Monitoring Board for review and correction. The Safety Analysis report will be approved by the DSMB chairman.

18 RESPONSIBILITIES

18.1 Investigational sites

18.1.1 Sites' qualifications

Investigators selected to participate in this study:

- must be qualified to conduct the clinical investigation in accordance to good clinical practice defined by ISO 14155:2020
- must possess adequate capacity to perform the study in terms of research set-up, equipment and co-investigators
- must be willing to accept the responsibilities of an investigator, including supervising test procedures and use of the investigational device
- must allow the sponsor's designated monitors and representatives to review all records pertaining to this study, including source documentation such as patient informed consents
- must allow potential internal or external quality assurance visits (by regulatory agencies such as EU Notified Bodies and Competent Authorities, the Australian TGA, the US FDA, other Health Authorities, Ethics Committees or sponsor with regards to audits)

Before participating in the study, all investigators must agree to adhere to and fulfil the terms of this investigational plan by the means of a signed and dated investigator's agreement and the signed and dated Protocol Statement of Compliance.

18.1.2 Necessary training and experience

Training on the investigational device will be provided by SENSOME at each site during the on-site Site Initiation Visit.

Training consists of:

- Step 1: Theoretical session:
    - A theoretical session: PowerPoint presentation wherein the features of the devices are clarified and how to prepare the device for use, how to use it in study patients and what to do after use. Specific attention is given to trouble shooting and the use of the device in relation to commercially available devices. This theoretical training includes pre-recorded videos about all steps.
    - Who to attend: all neurointerventionists who will be involved in the Endovascular Thrombectomy involving study patients.
    - Duration: 60 to 90 minutes
    - Trainer: Clinical Field Specialist of the sponsor
- Step 2: Practical session
    - A practical session: hands-on session with the study device in a transparent flow model. The flow model has features to:
        - Train on the mechanical features of the study device simulating tortuous vasculature
        - Train on the electrophysiological features of the study device using material that will simulate a clot.
        - The flow model can be used under fluoroscopy to maximize the learning
    - Who to attend: all neurointerventionists who will be involved in the Endovascular Thrombectomy involving study patients.
    - Duration: 30 to 45 minutes per neurointerventionist.
    - Trainer: Clinical Field Specialist of the sponsor

  Validation: the trainer will assess if the neurointerventionists who will be involved in the Endovascular Thrombectomy involving study patients has understood the theoretical training and is comfortable with the manipulation of the study device in the flow model. The training validation will be recorded in the Study Training Log.

- Step 3: On-site case support
    - Case support will be provided during study treatment of at least the first 2 study patients.
        - Discuss the different steps in the use of the study device, before arrival of the potential study patient in the procedure room.
        - Once the informed consent has been obtained, observe the preparation of the study device and give guidance if needed
        - Observe the use of the study device and give guidance if needed
        - Observe the disposal of the study devices and give guidance if needed
    - Who to attend: neurointerventionist doing the procedure
    - Duration: duration of preparation and the Endovascular Thrombectomy (EVT) procedure
    - Trainer: Clinical Field Specialist of the sponsor. However, this person will not handle any equipment that is in direct contact with the subject.

- Step 4: Remote Case support
    - Once a potential study patient is about to arrive at the hospital, the investigator or delegate is to inform the Clinical Field Specialist of the sponsor.
    - This Clinical Field Specialist will be stand-by for the whole duration of the (preparation of) the Endovascular Thrombectomy in case the treating physician has questions.

Validation: During Step 3 and Step 4, the trainer will assess if the neurointerventionists (who will be involved in the Endovascular Thrombectomy involving study patients) had demonstrated that she/he has achieved the competencies to perform the study procedure without SENSOME's Case Support. Once the investigator has demonstrated that he/she can prepare, use and dispose the device without Case Support, SENSOME will confirm that the training has been successfully completed.

18.2 INVESTIGATOR'S RESPONSIBILITIES

The principal investigator at each clinical site will have the following responsibilities:

- Obtain EC approval
- Supply the sponsor with his/her updated curriculum vitae and that of the co-investigators
- Obtain informed consent from patients
- Enroll patients and perform medical procedures
- Adhere to the clinical investigation plan
- Follow-up patients through to the end of the investigation plan
- Complete CRFs in English on time, legibly, completely, and accurately
- Report adverse events
- Maintain patient records and provide reports according to regulations
- Share all relevant study-related information with the associated co-investigators
- File and archive study documentation as per the local regulations
- Supervise testing and use of the investigational device
- Allow the sponsor's designated monitors and representatives to review all records pertaining to this study including source documentation such as patient informed consents
- Allow internal or external quality assurance visits (by the sponsor, the Ethics Committees and / or regulatory agencies) and notify the sponsor as soon as information on a planned audit / inspection is received.

18.3 SPONSOR'S RESPONSIBILITIES

The sponsor of this study is responsible for the following:

- Selection of the clinical investigators
- Obtain approval to begin the study, if required

- Development of clinical investigation plan (CIP), CRFs and any other study related documents
- Obtain agreements pertaining to the study with investigators/hospitals
- If applicable, also obtain agreements with clinical research organizations (CROs), and other involved parties
- Development and/or approval of an adequate informed consent form
- Ensure training on the study protocol and procedures
- Supply investigational devices and adequate documentation to investigational sites
- Provide study documentation and CRFs to investigational sites
- Ensure that appropriate information is given to the clinical investigators
- Database management, and maintenance
- Inform investigator of his/her responsibilities
- Maintain study records and provide reports according to regulations
- Ensure that the adverse event reports are reported by the clinical investigators in a timely and accurate manner and are forwarded to the relevant authorities (ethics committee and or regulatory bodies)

18.3.1 Financial Responsibility

This study is supported by the financial provisions of SENSOME.

Between the sponsor (or its local representative) and the Investigator's institution a written agreement (detailing the rights and obligations of each party) will be executed prior to the start of the study. The agreement will list all financial compensation for all study related activities that are not part of the normal daily practice in the institution. Compensation is following the applicable local fair market value compensation for these activities.

19 MONITORING

The purpose of the monitoring is to verify, that the conduct of the clinical investigation complies with this protocol (or subsequent amendment, the international standards and the applicable regulatory requirements).

19.1 MONITORING PROCEDURES

The sponsor and/or their designee will oversee the progress of this clinical trial and ensure it is conducted, recorded, and reported in accordance with: The Clinical Investigation Plan, standard operating procedures, applicable country specific regulatory requirements and the International Conference for Harmonization Good Clinical Practice (ICH-GCP), the ISO 14155 (2020) regulations and guidelines. Protecting the rights of Subjects, the safety of Subjects, and the quality and integrity of the data collected and submitted.

Site visits consist of site qualification visits (SQV), site initiation visits (SIV), site monitoring visits (MV), and close-out visits (CoV) performed on-site. In addition, sponsor may also perform remote visits keeping patient's privacy guaranteed during the preparation, the conduct and after the remove visit (as per local practices)

Site initiation, monitoring, and close-out visits must be confirmed with the clinical sites prior to the visit using a confirmation letter. Following the visit, a follow-up letter shall be used to document the activities performed and issues detected and shall be sent to the clinical site. Any essential documentation (or copies) retrieved during these visits must be filed into the Trial Master File (TMF).

The Principal Investigator and Site Personnel will ensure all data is accurate and study documents and subject data is available. The sites will be monitored by trained monitors to ensure the ensure accuracy of data, timeliness of data submissions, adequate Subject enrolment, investigational device accountability (if applicable), compliance with applicable laws and regulations, compliance with the protocol, compliance with the signed investigator agreement, and compliance with EC conditions and guidelines. The monitor will perform monitoring visits as outlined in the monitoring plan. The study monitor shall inform the Sponsor of any issues related to facilities, technical equipment or medical staff at the study centers. The Principal Investigator and/or designee shall permit and assist the study monitor in the verification of completed CRF against data in the source documents.

A monitoring plan will be used to detail the roles and responsibilities of the study manager and the study monitor. All monitoring activities will be conducted according to the Clinical Investigation Plan, ICH GCP Guidelines, EN ISO 14155:2020 (and all subsequent versions), and all applicable regional regulations and any study specific processes developed by the sponsor or its designees.

- On-site visits shall be conducted throughout the study to verify:
- Protection of the rights, safety, and welfare of patients;
- That the clinical study is being conducted in accordance with the CIP, agreement(s), and applicable regulations;
- Proper use of the clinical study device;
- Adverse events and clinical study non compliances are reported;
- Quality and integrity of the clinical study data.

When required by local site policies, remote monitoring may substitute for on-site monitoring visits. During the trial the study monitor will review all Patient Information and Consent Forms (PICFs) and the process for obtaining the subject's consent. The study monitor shall also be responsible for notifying such deficiencies, in writing, to the related site's Principal Investigator and convene with the study center personnel for appropriate re-training and timely corrective actions.

The study monitor shall submit written reports to the Sponsor, after each monitoring visit or contact with the Investigator on site. A first monitoring visit must be performed as outlined in the monitoring

plan. Frequency and timing for other monitoring visits shall be determined by the sponsor based on rate of enrolment.

19.2 Site Close-out visit

The purpose of the Close out visit is to collect all outstanding study data documents, ensure that the Principal Investigator's files are accurate and complete, review record retention requirements with the Principal Investigator, make a final accounting of all study supplies, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study.

20 ETHICAL CONSIDERATION AND REGULATORY STANDARDS

20.1 Ethical principles, laws and regulations

This study will be conducted in accordance with the latest version of the Declaration of Helsinki, Good Clinical Practices, ISO 14155:2020 and data protection laws.

20.2 Ethics committees, and institutions

This study is to be conducted in accordance with applicable EC and Regulatory regulations. The investigator must obtain approval from a properly constituted EC and Regulatory Agencies. prior to initiating the study with re-approval or review at least annually (as per local practice).

In addition, the sponsor must have a signed clinical study agreement with the site prior to the start of the study.

20.3 Data monitoring committees

An independent Data Safety Monitoring Board (DSMB), also known as a Data Monitoring Committee (DMC), will be responsible for monitoring safety and performance aspects of the study. Rules of operation and responsibilities will be outlined in the DSMB Charter.

20.4 Steering committee

A Steering Committee may be installed. This Committee is composed out of key investigators from the study, scientific advisors and representatives of the sponsor.

The scope of the Steering Committee will be to advice on study specific items such as protocol review, site performance (including recruitment, compliance to study protocol and the applicable guidelines) and recommendations for protocol amendment.

20.5 Liability coverage

Subject indemnification and insurance will adhere to Victorian Managed Insurance Authority and Medical Technology Association of Australia requirements and to the applicable European requirements.

20.6 STUDY DOCUMENTATION RETENTION

Each investigator must archive study documentation for a period of 15 years after the study is terminated or completed. Regional requirements related to record retention must be followed.

In case of a transfer of the archives, the investigator must inform the sponsor of record transfer within 10 working days after the transfer occurs.

21 PUBLICATIONS AND PRESENTATIONS

Publications and presentations referring to this clinical study will be coordinated by SENSOME to allow the use of all available data. Publications/presentations will be in adherence with the study contracts and the Publication and Presentation Charter

The Sponsor shall retain ownership of all case report forms, data analyses, and reports, which result from this study. All information obtained as a result of the study will be regarded as confidential, until appropriate analysis and review by the Sponsor are completed.

The study sponsor will collect data in such a way that no subject can be identified in any published reports on the clinical study.

No communication or publication (irrespective of the medium used) concerning the study or its results may take place without the prior, written, signed agreement of the Sponsor.

The sponsor proposes a plan for communications and publications regarding the study (primary and secondary objectives, sub analysis) and potential sub studies. This charter will be communicated with all participating investigational sites prior to enrolment of the first patient in the study.

This plan may vary according to the progress of the study and will be communicated with the investigational sites.

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23 ANNEX 1 – REVISION HISTORY

[redacted]

Clinical investigation plan - CLOT OUT

Clinical investigation plan - CLOT OUT

Clinical investigation plan - CLOT OUT

Clinical investigation plan - CLOT OUT

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