Study name	**The SEPARATE Study**
Study Title	Impedance **SE**nsor evaluated in **P**eripheral **AR**tery dise**A**se for **T**issue d**E**tection
Protocol Number	SEN_PAD_1
Version	3
Date	1 September 2023

CLINICAL INVESTIGATION PLAN

	Name	Function	Date/Signature
Prepared by	Hans TIELEMANS	Clinical Expert	07-Sep-2023 DocuSigned by: Hans Tielemans 0CB84100DB29425...
Reviewed by	Alina LATUS	QA/RA lead	07-Sep-2023 DocuSigned by: E36A3A39E7F143E...
Approved by	Julie LAFAURIE	Clinical and Preclinical Lead	07-Sep-2023 DocuSigned by: 98CCEA2E8FFE4FA...

Version	Change[1]
1	Creation
2	Revisions: Clarification done based on validation's questions from the Belgian Competent Authorities
3	Revisions: Protocol adjusted following the recommendations from the Belgian Competent Authorities

[1] Detailed descriptions of and rational for changes can be found in Annex 1.

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1 Sponsor approval page

We confirm that this Clinical Investigation Plan (CIP) has been reviewed by medical doctors, experts in the field of interventional radiology. 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:
Alina LATUS Quality Assurance and Regulatory Affairs Lead	Julie LAFAURIE Clinical and Preclinical Lead

2 Statement of compliance

I confirm that this study will be conducted in compliance with the Clinical Investigation Plan, 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

Department	Name	Address	Contact Details
Principal investigator	Dr Koen Deloose, MD	Department of Vascular Surgery AZ Sint Blasius Kroonveldlaan 50 9200 Dendermonde Belgium	[redacted]
Sponsor / Urgencies	SENSOME	2-12 immeuble Odyssée 2 rue du Chemin des Femmes 91300 Massy FRANCE	[redacted]

4 List of abbreviations

Term	Definition
ABI	Ankle Brachial Index
ADE	Adverse Device Effect
AE	Adverse event
ALI	Acute Limb Ischemia
BLE	Bluetooth Low Energy
CA	Competent Authorities
CIP	Clinical Investigation Plan
CLI	Chronic Limb Ischemia
CSGS	Clotild® Smart Guidewire System
CTO	Chronic Total Occlusion
CT scan	Computed Tomography Scan
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
(e)CRF	(Electronic) Case Report Form
EVT	EndoVascular Treatment
IB	Investigator's Brochure
IVUS	IntraVascular UltraSound
LAR	Legally Authorized Representative
MRI	Magnetic Resonance Imaging
OEM	Original Equipment Manufacturer
PAD	Peripheral Artery Disease
PICF	Patient Information and Consent Form
RBC	Red Blood Cells
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TASC	TransAtlantic Inter-Society Consensus (on the Management of Peripheral Arterial Disease)
USADE	Unanticipated Serious Adverse Device Effect

5 Study summary

Title	The SEPARATE Study (Impedance **SE**nsor evaluated in **P**eripheral **AR**tery dise**A**se for **T**issue d**E**tection)
Protocol Number	SEN_PAD_1
Study Name	The SEPARATE Study
Study Device	Clotild® Smart Guidewire System (CSGS)
Purpose	The objective of the study is to evaluate the feasibility of the CSGS sensor to differentiate tissues involved in Peripheral Artery Disease (PAD).
Study type	Feasibility study
Study design	Prospective, Single-arm, Single-centre study
Number of patients and Clinical Sites	Up to 30 patients at one centre in Belgium – AZ Sint Blasius Hospital, Dendermonde, Belgium
Patient Population	Subjects presenting with PAD will be evaluated for study participation. Patients suffering from Chronic Total Occlusions or Acute Limb Ischemia will be included in this study. Up to 30 patients will be enrolled. Analysis of the data will take place on a continuous basis and will determine the to-be-enrolled number of patients.
Endpoints	**Primary Endpoint** The ability of Clotild® Smart Guidewire System to acquire electrophysiological measurements in the lesion and/or subintimal. **Secondary Endpoints** The ability of Clotild® Smart Guidewire System to differentiate various tissues involved in Peripheral Artery Disease such as, but not limited to: ○ arterial wall ○ subintimal area ○ clot (fresh / subacute / organised) ○ plaque (soft / hard) ○ hyperplasia

Eligibility criteria	**Inclusion criteria** Candidates for the study must meet the following inclusion criteria below: 1. Age > 18 years 2. Subjects with acute and chronic occlusions in the arteries of the lower limbs eligible for endovascular interventional procedures 3. Written Informed Consent to participate in the study. **Exclusion criteria** Candidates for this study will be excluded if ANY of the following conditions are present: 1. Target vessel aneurysm 2. Target vessel diameter <2mm 3. Lesions starting at the Common Iliac Artery 4. Any subject that is, according to the discretion of the investigator, not eligible for study participation 5. 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 6 months enrolment period **Follow-up duration** Per patient: 24hrs(-12hrs) post-procedure

6 Introduction

6.1 Purpose

The objective of the study is to evaluate the ability of Clotild® Smart Guidewire System (CSGS) to provide electrophysiological measurements of various lesion tissues involved in Peripheral Artery Disease (PAD) with the goal of improving patient's outcome.

Previously the CSGS was used in a clinical study in stroke patients (The Clot Out Study) to direct a catheter through blood vessels and to measure electrophysiological parameters in the blood vessels during procedures.

In the current study however, a commercially available CE marked guidewire will be used to direct a catheter through blood vessels while the Clotild® Smart Guidewire System will only be used to perform electrophysiological measurements in the blood vessels. It is thus designed for use as an adjunct to conventional angiographic procedures. Regarding the measurements, the CSGS is used solely to record impedance measurements of various relevant tissues. The interpretation of these measurements in terms of tissue type is not displayed to the user. As a consequence, the use of the Clotild® Smart Guidewire System has no effect on the PAD procedure, the physician not being able to modify his/her choice of treatment based on the CSGS display.

6.2 Medical background and PAD Management

In 2021, peripheral artery disease (PAD) affected over 230 million people worldwide and is responsible of 12 to 15% of deaths in Europe (Aday and Matsushita 2021). The PAD mainly affects lower limb, and it is in 95% caused by atherosclerosis[2]. Atherosclerosis is a slowly progressive disease leading to the narrowing of the artery lumen which becomes stenosed or completely occluded. At early stages, low density lipoprotein (LDL) will accumulate in the intima and lead to the adhesion of monocytes to the endothelium. The monocytes then migrate inside the arterial wall and differentiate into foam cells. At later stages, a necrotic core will developpe composed of apoptosis foam cells and smooth muscular cells (SMC) that release lipidic cells into the core and disrupt the intima. Then, SMC will migrate into the arterial wall and will multiply around the plaque and lead to pathological intimal thickening. Over time, a fibrous cap is formed and is composed of fibrous tissue, mostly with a high content of type I collagen. Calcifications are commonly found in advancing atherosclerotic lesions and tend to increase as individuals age. The plaque can rupture, known as "vulnerable plaque", exposing highly thrombogenic core to the blood and leading to thrombus formation (Tavallaei et al. 2018).

[2] Guideline on PAD from European Society for Vascular Medicine
https://www.portailvasculaire.fr/sites/default/files/docs/2019_esvm_aomi_recommandations.pdf

The onset can be[2]:

- chronic limb ischemia (CLI), due to atherosclerosis plaque formation. The development of symptoms and severity of the occlusion evolve over a few weeks to years. Symptoms go from asymptomatic to severe claudication and in worst case scenario to ulcer or gangrene leading to amputations.
- acute limb ischemia (ALI), due to a sudden narrowing of an artery provoking acute ischemia in the legs and pain for the patient. In 50% of the time, it is caused by thrombosis and 30% by an embolus. ALI needs to be treated immediately to avoid amputation.

Surgery (bypass surgery or thrombectomy) and endovascular treatment are performed to treat symptoms related to PAD and the choice of treatment depends on the clinical stage and severity of the disease. For now, it seems that there is no consensus regarding the best treatment options between open surgery and endovascular treatment, but endovascular treatment has gained wider acceptance by physicians and is recommended as a first line of treatment. The choice will also be based on patient's will[3]. In case of Chronic Total Occlusion (CTO), endovascular intervention failure rate goes to 20% because of the inability to cross the occlusion. In that case, subintimal navigation is used to cross the lesion before re-entry in the intraluminal space (Chang, Zheng, and Liu 2016).

Endovascular procedure includes percutaneous transluminal angioplasty (PTA) which consists of placing a balloon intraluminal through the lesion and expand it to upload pressure to break the lesion and thus restore the blood flow. A drug coated balloon might be used to introduce local medication to suppress neointimal hyperplasia (Kayssi et al. 2019) (Lazar and Morrissey 2020). Often stents are placed intra luminally where the stenose/occlusion occur and prevent the artery from re-closing. Stents can also be drug-coated to prevent from restenosis (Medical Advisory Secretariat 2010). Atherectomy is a technique used to prepare the artery for the insertion of a balloon or stent by removing plaque from the arterial wall. Unlike angioplasty and stent procedures, atherectomy involves the use of a rotating cutting blade to be used intra luminally (Lazar and Morrissey 2020).

ALI's patients require specific treatment. To dissolve the thrombus, catheter-directed thrombolysis is used at the site of the occlusion and can be combined with mechanical thrombectomy. If those procedure aren't successful, surgical revascularization is an option (Olinic et al. 2019).

Plaque characterization is poorly described prior and during intervention. Nowadays images are providing information about length, percentage of stenosis or occlusion and presence of calcium. This information already influences the physicians' choice of treatment approaches. More information on morphology and composition of the plaque could help the physician's approach regarding device

[3] Guideline on PAD from European Society for Vascular Medicine
https://www.portailvasculaire.fr/sites/default/files/docs/2019_esvm_aomi_recommandations.pdf

selection during endovascular intervention. A study collected information on which type of device is to be used in relation to the plaque's morphology (Roy, Dueck, and Wright 2016).

In the last decade, a new imaging method called IntraVascular UltraSound (IVUS) has been developed. It is used as an adjunct during endovascular procedures and provides three-dimensional information on the vessel. It provides physicians with information about the morphology of the plaque, vessel diameter, and the presence of artery dissections. This information guides the endovascular intervention and helps in choosing the right treatment device. However, the use of IVUS requires installation of material at the hospital and training for all medical personnel to navigate and interpret the images thus adding cost and procedure time (Loffroy et al. 2020).

Techniques involving electric impedance spectroscopy (Süselbeck et al. 2005) have attempted, with promising results, to measure impedance in atherosclerotic plaque to differentiate healthy arterial wall versus atherosclerotic plaque and type of plaque.

Because SENSOME's miniaturized technology, based on Electrochemical Impedance Spectroscopy (EIS) and easily mounted on low profile endovascular devices, might be able to distinguish between various tissues (like smooth muscle cell rich tissue, red blood cells rich tissue, platelets rich tissue, acellular tissues…), few use cases are foreseen of specific interest for its use in PAD endovascular treatment:

- the assessment of the age of a clot (fresh vs old) guiding the treatment approach to avoid resistance to treatment;
- the differentiation between subintimal and luminal navigation when crossing a lesion, therefore helping the re-entry phase and informing for contraindications of specific treatments (like atherectomy);
- and potentially the characterization of plaque.

The SEPARATE study aims at confirming the potential of SENSOME's technology in PAD treatment and identifying the most promising and clinically useful use cases.

7 Benchmark of comparable devices

The purpose of the benchmark device is to illustrate the use of a similar product currently on the market with similar principle of operation and similar intended purpose. The benchmark device is not to be considered an equivalent device and will therefore only serve as a comparator to the Clotild® to further describe the current acceptable benefit/risk profile that is identified in the State-of-the-Art section in the Clinical Evaluation Report. [redacted]

[redacted]

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 System (CSGS) was designed as a neurovascular guidewire equipped with SENSOME's proprietary impedance sensor. The latter allows the measurement of electrophysiological characteristics of the surrounding fluid or tissue.

IMPORTANT

For its use in peripheral endovascular procedures, Clotild® should not be used as a guidewire to navigate and/or cross lesions but only to bring the sensor in contact with the tissues to be measured, once the navigation has been done with commercially available medical devices.

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.

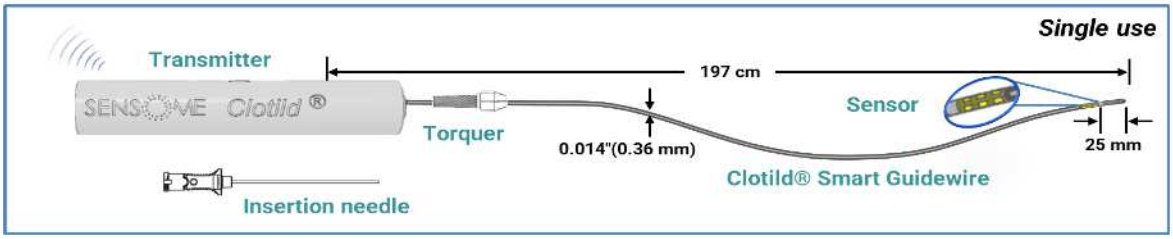


Figure 1: Clotild® Smart guidewire System overview

8.1.1 Clotild® Smart Guidewire

The Clotild® Smart Guidewire has a standard 0.014'' (0.36 mm) diameter and 2 m length.

[redacted]

Figure 2: Schematic view of the Clotild® Smart Guidewire's cross-section

[redacted]

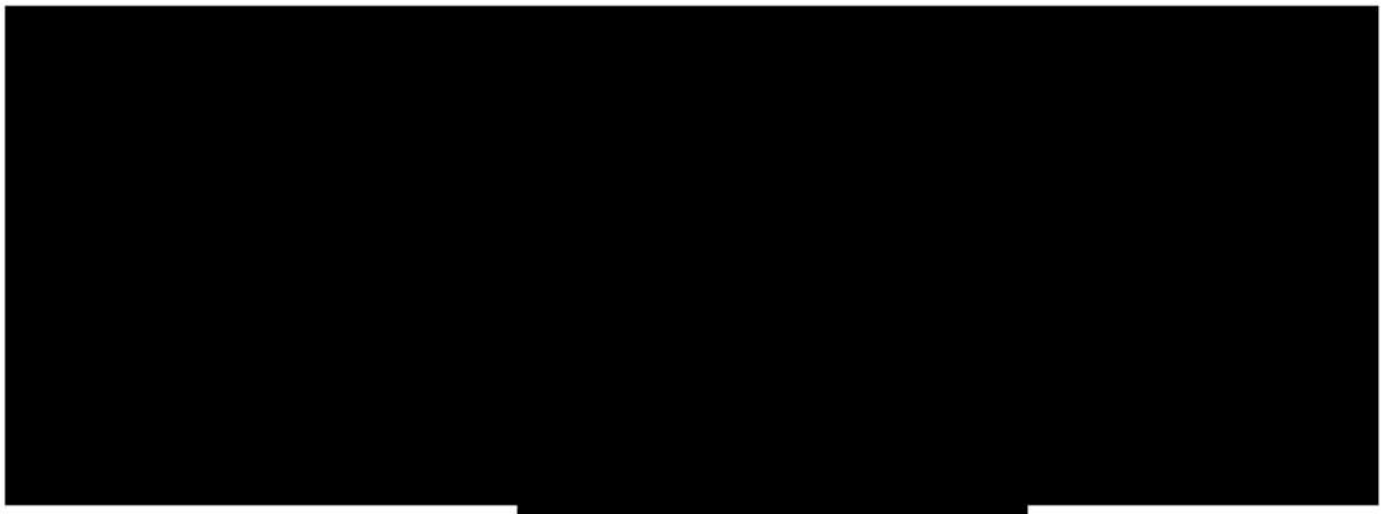
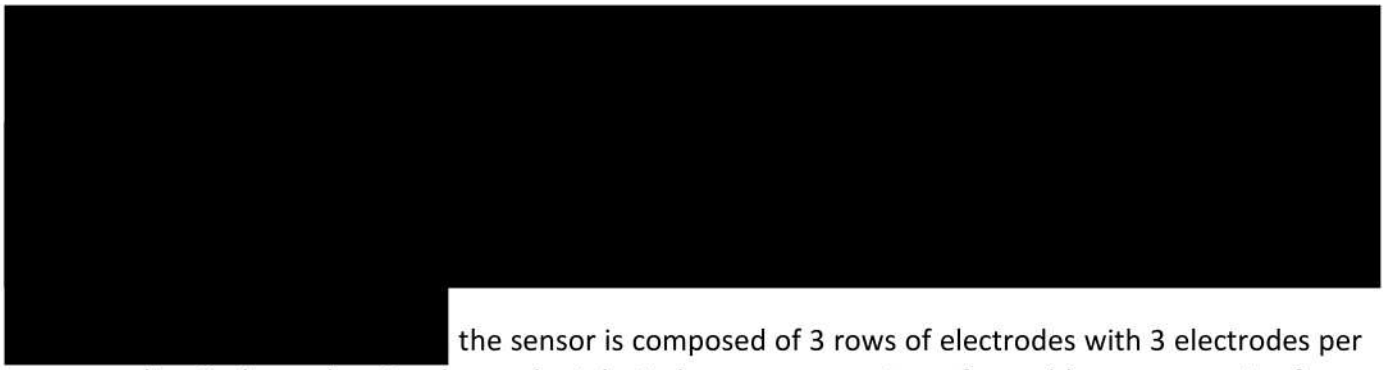


Figure 3:



the sensor is composed of 3 rows of electrodes with 3 electrodes per row, totaling 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 individual measurements of a single raw (2 to 3 electrode pairs) is defined as the '**row scale**'. The aggregation of the 9 individual measurements, consisting in a full acquisition by the sensor, is defined as the '**sensor scale**'. For neurovascular occlusion probing, an aggregation of all measurements performed all along the occlusion might be relevant to reconstitute an analysis of the whole clot. In that case, the aggregation of all measurements is defined as the '**clot scale**'.

Figure 4: 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.

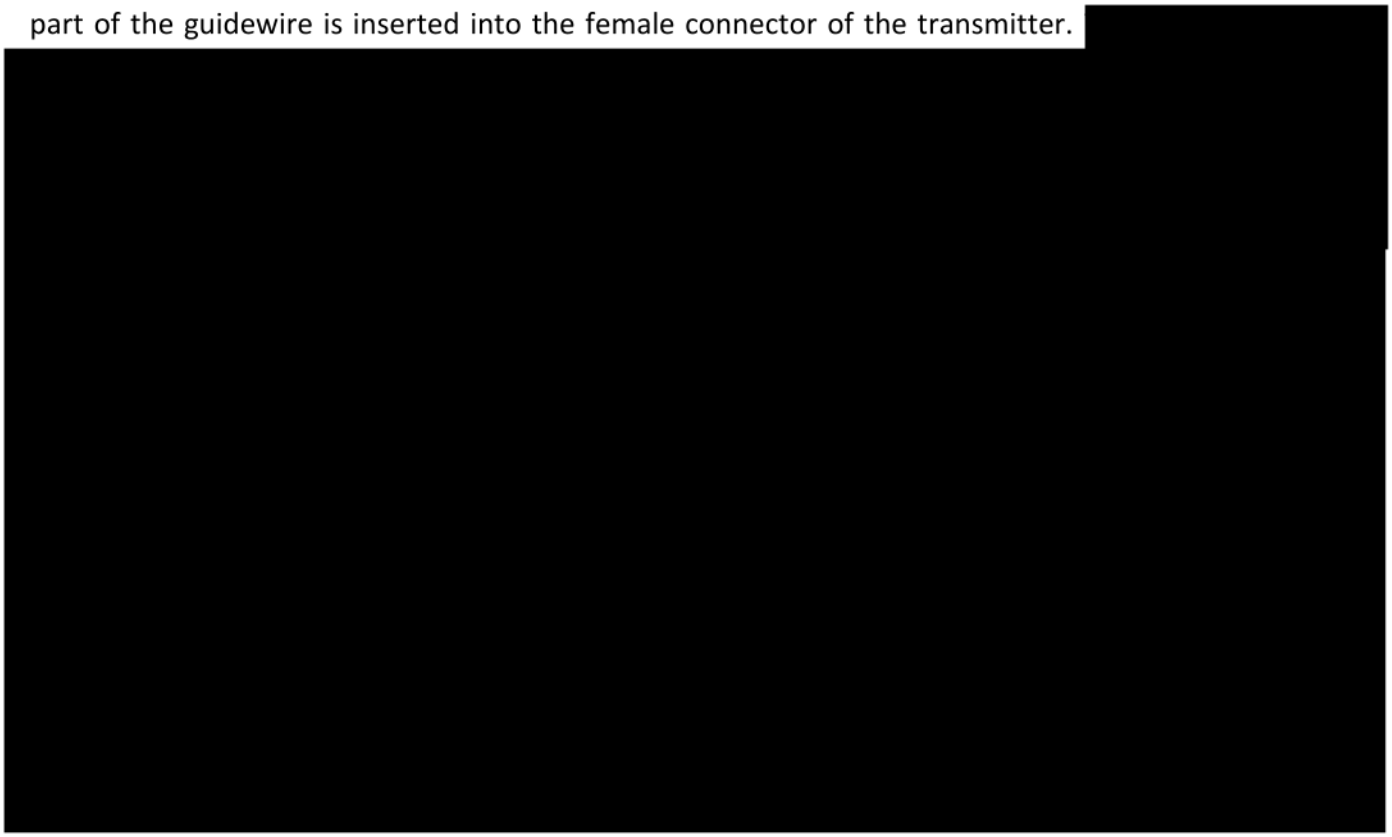


Figure 5: Clotild® Smart Guidewire Transmitter

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 6). The tablet is supplied with a Bluetooth USB dongle that provides wireless communication with the transmitter. The tablet hardware is supplied by

Figure 6: Medical Tablet with Cloviz® Software

8.2 Intended use

8.2.1 Previous intended use of CSGS

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.

8.2.2 Intended use of CSGS in PAD

Intended Use

Clotild® Smart Guidewire System is designed to perform electrophysiological measurements in the blood vessels during peripheral endovascular procedures. It is designed for use as an adjunct to conventional angiographic procedures.

Indication of Use

Clotild® Smart Guidewire System is indicated for peripheral endovascular use.

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
- 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.

8.4 Device Return

All used study devices will be returned to SENSOME. The sponsor will provide instructions and shipping materials (biohazard bag etc.). In particular, study device(s) with a reported device deficiency/device malfunction will be investigated/analysed by the manufacturer.

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

8.5 Pre-clinical testing

In order to provide evidence that the device under study is sufficiently safe and performant for human experience, pre-clinical testing, including animal studies, were performed and are described in detail in the Investigator's Brochure (*CLI_INVEST_BROCH_CSGS_PAD_V1 or later version*). These tests cover:

- Evaluation of biological safety
- Evaluation of mechanical safety
- Evaluation of electrical safety
- Cloviz® software validation
- Preliminary prediction performance tests
- Animal studies, including safety and performance evaluation
- Benchtop model testing to assess electrical robustness
- Usability tests

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 current trial.

Based on the results of pre-clinical testing, it was concluded that Clotild® Smart Guidewire System is safe for use in a clinical study environment. A First-In-Human study was initiated where the device is used in cerebral arteries (see next section).

8.6 Clinical testing

SENSOME is performing a First-In-Human clinical study in Acute Ischemic Stroke (AIS) patients, The Clot Out study.

The goals of The Clot Out study are to evaluate (1) the safety of using Clotild® Smart Guidewire System (CSGS) at the occlusion location during mechanical thrombectomy procedure for the treatment of

subjects with acute ischemic stroke and (2) the performance of CSGS (defined here as the feasibility to measure electrophysiological properties of the occlusion).

This study is still ongoing. To date, the CSGS has been used in thirty-one subjects. The Data and Safety Monitoring Board has met several times and did determine that there are no safety concerns and the study enrollment can continue as scheduled.

9 Study Design and Population

9.1 Study design

This study is a prospective single arm, one centre feasibility study.

9.2 Eligibility criteria

9.2.1 Inclusion criteria

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

1. Age > 18 years
2. Subjects with acute and chronic occlusions in the arteries of the lower limbs eligible for endovascular interventional procedures
3. Written Informed Consent to participate in the study.

9.2.2 Exclusion criteria

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

1. Target vessel aneurysm
2. Target vessel diameter <2mm
3. Lesions starting at the Common Iliac Artery
4. Any subject that is, according to the discretion of the investigator, not eligible for study participation
5. Known lactating or confirmation of positive pregnancy test according to site specific standard of care (e.g. test, verbal communication).

10 Study Objective

The objective of the study is to evaluate the feasibility of the CSGS sensor to differentiate tissues involved in Peripheral Artery Disease (PAD).

11 Study Endpoints

11.1 Primary Endpoint

The ability of Clotild® Smart Guidewire System to acquire electrophysiological measurements in the lesion and/or subintimal.

11.2 Secondary Endpoints

The ability of Clotild® Smart Guidewire System to differentiate various tissues involved in Peripheral Artery Disease such as, but not limited to:

- arterial wall
- subintimal area
- clot (fresh / subacute / organised)
- plaque (soft / hard)
- hyperplasia

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 analysis 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 benchmark devices

It is well-known that guidewires play a crucial role in several medical disciplines because they facilitate passage through various luminal structures. However, the clinical data available today on the Transend® devices is very scarce, being limited to a case report (Darsaut et al. 2014).

In fact, to date, there is no official consensus about which guidewires shall be used during intervention, being all the related information retrieved from common practice and interventionists own's clinical experiences. Although not centered on the Transend® benchmark device, the review by Kipling et al. (Kipling, Mohammed, and Medding 2009) offers a high-level overview of the current standards on guidewire use, together with a summary of the most common device-related complications, which appear to be relatively low when compared to the number of interventions carried out that use such devices.

Accordingly, the 3-year incident data search yielded only 64 records for the Transend® product in MAUDE, of which only 7 were classified as injury. Importantly, no deaths were associated with the product since 2017. Hence, despite the paucity of clinical data, the Transend® product is commonly used in clinical practice (Harrigan and Deveikis 2018) and it can be concluded that its use is associated with a relatively low incidence of AEs.

The amount of clinical data available today for the Eagle Eye™ Platinum ST is limited to information published at websites of Competent Authorities in USA (FDA). Only the MAUDE search yielded significant results, which further supports the low incidence of AEs associated with this device. Among the device-related failures reported, it is worth stressing that the significant proportion of communication/transmission problems between the sensor and the external hub can result in non-displaying of the images on the screen, material separation, and the entrapment of the device, despite not substantially jeopardizing the clinical outcome.

12.2 Risk minimization

12.2.1 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).

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.

The complete risk analysis is presented and discussed in the Risk Management Report (*QRM_RMR_Smart_Guidewire_PAD_V1 or later version*).

This document contents but is not limited to:

- The count of individual initial risk before mitigation,
- The count of individual residual risk after mitigation,
- A description of the mitigation of the risks,
- The benefit/risk analysis,
- A conclusion on the overall risk residual acceptability.

Information regarding known or foreseeable risks, any undesirable effects, contraindications and warnings are detailed in the Instructions For Use (*DND_IFU_CSGS_PAD_V1 or later version)* and comes from the risk analysis.

12.2.2 Risk minimization during study start-up

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

- The sponsor will select investigational site(s) that have demonstrated to be experienced in conduct of clinical studies with innovative technologies.
- Sufficient experience in interventional radiology.
- 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 a monitor 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 and or diagnostic probes. Please refer to section 17.1.2 Necessary training and experience for more details on the provided training.

12.2.3 Risk minimization during the study

The sponsor will employ the following measures throughout the course of this investigation to minimise 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 (minimum 1), 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 on a regular basis and as defined in the DSBM charter.

- 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.
- The SENSOME Clinical Field Specialist may attend the procedure and advice the investigator during the use of the study device.

12.2.4 Rules for temporary enrolment suspension

The CSGS will be used for its sensor features only. It should not be used as a guidewire to navigate and/or cross lesions but only to bring the sensor in contact with the tissues to be measured, once the navigation has been done with commercially available medical devices.

In case >1 dissection (that could not be attributed to use of the CE marked guidewire of choice of the investigator) occurs within the first 5 subjects, study enrolment will be temporary suspended to investigate.

Also, in case >2 dissections (that could not be attributed to use of the CE marked guidewire of choice of the investigator) occur within the first 10 subjects, study enrolment will be temporary suspended to investigate.

The DSMB will assess the event(s) and will advice to:

1) Give approval to resume enrolment.
2) Will request the sponsor to perform additional investigations before assessing if it is safe to resume enrolment.
3) Will advice the sponsor to stop further study enrolment.

12.3 Benefit vs Risk Assessment

CSGS has been designed to identify the nature of lesion composition in situ and in real time during intervention. In the future, CSGS will provide physicians with information on the nature of the lesion which will allow them to make an informed choice on the most effective therapeutic option.

In the framework of this feasibility study, information on the lesion will not be provided to the physicians to aid the decision making on the device to be used. Upon completion of the study, data collected may benefit the future patients at large, through helping physicians to choose the most effective therapeutic approach.

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 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 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.

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. If the patient is eligible, the investigator will do due diligence to explain the study (and study procedure) and the associated risks and benefits of participating to the patient. The patient 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 his/her participation. 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 is 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.

The Informed Consent Form may be dated and signed by the patient any time prior to the Screening Visit assessments. If this is >4 weeks prior the Screening Visit assessments, the patient will be requested to date and sign the form again prior to screening to confirm participation in the study.

13.3 Point of Enrolment

Point of enrolment: Patients are considered as enrolled once the patient has signed and dated the patient informed consent form as part of the informed consent process.

13.4 Procedural success

Procedural success is defined as the ability of CSGS to acquire at least one non-anomalous impedance measurement of the lesion.

13.5 Screen Failures

Patient having signed the informed consent form but however eligibility has not been confirmed on the day of the procedure is being considered a screen failure.

13.6 Schedule of Assessments

The investigator is responsible for screening all potential patients and selecting the patients meeting the inclusion/exclusion criteria. As from informed 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.

Parameter/Examination	Screening[4]	Procedure	24hrs (-12hrs.) Post-procedure
Inclusion/Exclusion criteria	X	X[5]	
Patient Information/ informed consent[6]	X		
Physical examination (<2 weeks)	X		
Demographics & medical history including time of claudication onset and Rutherford classification	X		
Pregnancy test[7]	X		
Vital Signs	X	X	
Ankle Brachial Index (ABI) (<3 months)	X		

[4] To take place ≤4 weeks prior to the study procedure
[5] Eligibility to be reconfirmed prior to the study procedure
[6] If ICF was obtained >4 weeks prior to the screening visit, the patient will reconfirm his willingness to participate in the study by signing and personally dating the document again
[7] According to the hospital's normal daily practice

Imaging exams	Echo / CT / CTA[8]	DSA[9]	
Study procedure		X	
AE/SAE		X	X
Concomitant medication	X	X	X

13.7 Screening visit

The Screening Visit Assessment do not have to be done at the same day. However, all study assessments have to take place ≤4 weeks of the study procedure.

- Full physical examination will be repeated if it was done ≥2weeks prior to the procedure.
- Medical history will be limited to relevant medical history only (cardiovascular, endocrino, PAD, skin).
- Pregnancy test will done according to site specific standard of care (e.g. test, verbal communication).
- Vital signs include: blood pressure, heart rate.
- Ankle Brachial Index will be measured within 3 months of the study procedure.
- Rutherford classification.
- Imaging will be done according to the normal practice and within 4 weeks of the study procedure.
- Collection of concomitant medication includes all medication since admission at the hospital.

13.8 Procedure

The PAD endovascular treatment will be performed as per normal clinical practice with the exception of the study procedure described below.

- Patient's eligibility will be confirmed prior to the study procedure. In the case eligibility is not confirmed, this will be determined as a Screen Failure. No more information will be collected from this patient and the study exit CRF can be completed.
- Vital signs include: blood pressure, heart rate.
- Imaging, including Digital Substracted Angiography (DSA), will be collected by the sponsor.
- Information regarding lesion characteristics (length, location, calcification level, etc…) and the endovascular procedure (devices used, navigation path, etc…) will be collected.
- The **study procedure** will take place during the PAD endovascular treatment (PAD procedure) and includes the following:

[8] If available according to the hospital's normal practice, within 4 weeks of study procedure
[9] Images will be collected by the sponsor

- Preparation of the study device, including installation of the tablet.
- Insertion of the study device in the sheath.
- Making the electrophysiological measurements: at least one reference measurement in blood and one measurement in the lesion. Acquisitions can be performed at several locations to target the various tissues of interest. Note that the interpretation of the measurement in terms of tissue type is not displayed to the user. As a consequence, the use of the Clotild® Smart Guidewire System has no effect on the PAD procedure, the user not being able to modify his/her choice of treatment based on the CSGS display.
- Removal of the study device from the sheath.

- (Serious) Adverse Event collection will start once the eligibility has been confirmed.
- Collection of concomitant medication includes all medication used during the PAD procedure.

13.9 Follow-up

Follow-up will take place at 24hrs (-12hrs).

- New Adverse Event will be collected until 24hr (-12hrs) post procedure.
- Collection of new concomitant medication will end at 24hrs (-12hrs).

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.
- Adverse Events: at the end of the study, the outcome of each adverse event will be assessed.
- Serious Adverse Events will be followed-up until the event resolved or a stable outcome was observed or until 7 days post procedure, which occurs first.

14 Statistical consideration

This is a single-centre, non-randomized, prospective, feasibility study designed to evaluate the feasibility of the CSGS sensor to differentiate tissues involved in subjects with PAD.

Additional details of the analysis will be provided in the Statistical Analysis Plan.

14.1 Statistical Analyses

In the SEPARATE study, the user is invited to record impedance measurements at various relevant locations during an interventional PAD procedure. Considering that the secondary endpoint of the study is to evaluate the feasibility of developing predictive models that will discriminate various tissue types, the interpretation of the measurements collected during the SEPARATE study cannot be displayed to the physician during the study. As a consequence, the use of the Clotild® Smart Guidewire System has no effect on the PAD procedure, the user not being able to modify his/her choice of treatment based on

the CSGS display. For this reason, the design of the study does not include randomization or control group or blinded arm.

Due to the exploratory nature of the trial, analysis of the trial data will be performed on a continuous basis. No hypotheses are set forward. The collected data will serve only for the exploratory purpose and will be used to develop statistical models to differentiate tissues.

14.2 Analyses population

At most 30 subjects with PAD will be enrolled in one site for this study.

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.

Treated Population

All patients in which the guidewire went through the sheath. This population will be used for safety evaluation.

Performance Population

To evaluate the sensor's ability to differentiate tissues, only data from subjects for which at least 1 non-anomalous acquisition in the lesion was captured by the CSGS will be used. The evaluation of tissue differentiation capabilities (see secondary endpoints) will be performed on this population set.

14.3 Endpoint analysis

14.3.1 Primary Endpoint analysis

The primary endpoint is the ability of Clotild® Smart Guidewire System (CSGS) to acquire electrophysiological measurements in the lesion and/or subintimal. Data of the 9 individual impedance measurements will be collected during the procedure and might be aggregated at the row level or sensor level (see Figure 4). This endpoint represents the procedural success rate - procedural success being defined as the CSGS obtaining at least one non-anomalous impedance measurement in the lesion (see section 13.4) during the procedure. Given the feasibility nature of the study, a success rate of 60% is expected.

Data coverage will be calculated.

14.3.2 Secondary Endpoint analysis

Secondary endpoints are the ability of Clotild® Smart Guidewire System to differentiate various tissues involved in Peripheral Artery Disease such as, but not limited to:

- arterial wall
- subintimal area
- clot (fresh / subacute / organised)
- plaque (soft / hard)
- hyperplasia

The ability to differentiate tissues will be reported by descriptive statistics.

To further assess the secondary endpoint, Machine Learning analysis will be applied. Following standard procedure, features will be extracted from the impedance measurements and used for model inference. To address potential data leakage, models will be evaluated in a Leave One Patient Out Cross Validation manner and feature preprocessing will take place within each fold (e.g.: subtracting the median and dividing by the interquartile range to scale the features). Since class imbalance is expected given that not all patients will provide the same tissues, metrics that are not affected by skewed class distribution will be evaluated (e.g.: micro-averaged f-beta score).

***14.3.3** Sensitivity analysis*

An additional sensitivity analysis will be conducted as a secondary examination of the primary analysis for primary and secondary endpoints. This sensitivity analysis will be performed in patients with acute limb ischemia since the tissue in these patients is thought to be composed of more red blood cells compared to patients with chronic total occlusions. The need for additional sensitivity analyses in other types of tissue will be explored during the conduct of the study.

14.4 Study sample size calculations

The maximal total sample size is set at 30 subjects. Since this trial is an exploratory feasibility study, the sample size does not have to be statistically driven since there is no hypothesis. On top of that, it is possible to collect large sample of data sets from a small sample of study subjects thanks to the 9 electrodes arrays of the sensor (see Figure 4) and the possibility to collect multiple measurement points during the procedure (see section 13.8). Previous experience from the Clot Out study showed that a sample size of maximally 30 subjects will be enough to evaluate the feasibility of the CSGS sensor to differentiate tissues.

14.5 Missing data

Every effort will be undertaken to fulfil all the requirements of the clinical investigation plan concerning the collection and management of data. No imputations of missing data will be done.

Regarding the impedance measurements captured by the CSGS, data might be missing or anomalous having an impact to the endpoints. Based on the Device Deficiency rate in a previous study (The Clot Out Study), the estimated amount is 40%. The missingness/anomaly might be due to the following reasons:

- Technical malfunctions, leading to missing data or anomalous data, among which device deficiency due to electrical connection dysfunction;
- Use error leading to missing data because measurements have not been acquired or to anomalous data because the sensor was covered by the catheter while the measurement was acquired.

The criteria to discard anomalous measurements 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 analysis.
- 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 the reference measurement to the first lesion measurement is considered anomalous; all remaining measurements made with this electrode pair will be excluded from the dataset.
- Anomalies related to invalid reference measurements are reported as too-high dispersion across electrode pairs in the reference measurement. Persistence of the anomaly till the first lesion measurement requires exclusion from all measurements from the concerned electrode pairs.

14.6 Bias

To minimize bias, a DMSB will be installed to oversee the conduct of the trial. The DSMB 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 to allow a comprehensive review.

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.

15 Study Conduct and Management

15.1 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.

15.2 Amendments

The dataset that will be constructed during this clinical investigation should serve to develop prediction models. Besides this study, SENSOME has other projects providing input to these prediction models. 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 Study Report.

15.3 Data management

A validated CRF (paper or electronic) will be used to collect clinical data for this study. The investigator and site staff will be trained on the use of the CRF. An explanation for the omission of any required data should appear on the appropriate CRF page or other data collection forms.

The CRF 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 CRF 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 CRF 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.

In the case an external data management organisation will be involved in the study: after database lock, 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;
- CRF contents;
- 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.

15.4 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.

15.5 Protocol deviations

A protocol deviation is defined as an event where the 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 study objectives;
- Follow-up being performed outside the protocol specified visit window.

15.6 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 CRF 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.

15.7 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.

At the end of the clinical investigation the sponsor must notify the competent authority within 15 days, provide justification in case of a temporary halt or early termination. In case of a halt due to safety grounds, the sponsor will inform the competent authority within 24 hours.

The end of the clinical investigation must coincide with the last follow up visit for the last patients. Within one year of the end of study, a report must be submitted to the competent authority by the sponsor or, in the case of an early termination or temporary halt, within 3 months.

15.8 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.

16 Safety Management

16.1 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.
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.

16.2 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.

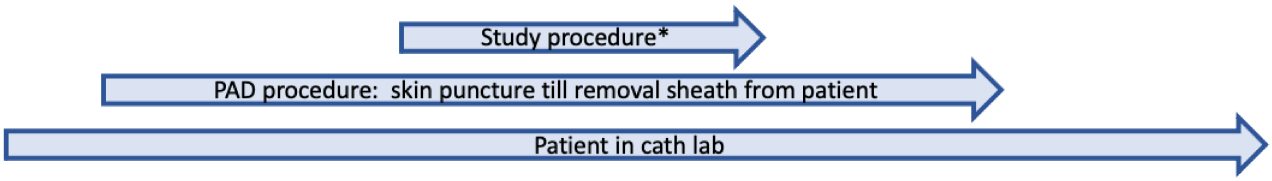
Moderate: interferes with the patient's usual activity and/or requires symptomatic treatment.

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

16.3 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 study device
- the study procedure (from preparation of the tablet and study device till last removal from the sheath)
- the PAD procedure



*Study Procedure: preparation tablet till removal study device from sheath

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 PAD 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 PAD 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 PAD procedure seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship:

The event is associated with the investigational device or to the study procedure or to the PAD 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 procedure/PAD procedure and the Adverse Event.

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

16.4 Adverse Event Reporting by Investigator

Adverse Events

All Adverse Events are to be reported via the CRF 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 CRF. The CRF must be scanned and send by email to the sponsor. The site must provide additional information, if required by the sponsor or designee.

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 and/or procedure 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.

16.5 Reporting of adverse events to Ethics Committees and Regulatory Authorities

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

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 and/or the investigation procedure or where such causal relationship is reasonably possible.
   Note: 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).

Pending the availability of Eudamed in Belgium, the Sponsor must report all SAEs to the FAMHP at ct.rd@fagg.be using the European form.

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[10] 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.

16.6 Device deficiencies Reporting by Investigator

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

Device malfunctions and use errors should be reported without unjustified delay (within 24 hours) via the CRF and by e-mail to the sponsor and its designee. In the case of a device deficiency or malfunction, the study device must be returned to the sponsor for analysis as soon as possible.

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

16.7 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 CRF.

16.8 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 to the study procedure or to the PAD procedure (study procedure excluded).

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

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.

17 Responsibilities

17.1 Investigational sites

17.1.1 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 clinical investigational plan by the means of a signed and dated investigator's agreement and the signed and dated the Statement of Compliance (section 2).

17.1.2 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.
    - Who to attend: all medical doctors who will be involved in the study procedure involving study patients.

- Duration: 30 minutes
- Trainer: Clinical Field Specialist of the sponsor

- Step 2: Practical session (optional)
  - 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
    - Train on the electrophysiological features of the study device
    - The flow model can be used under fluoroscopy to maximize the learning
  - Who to attend: all interventionists who will be involved in the study procedure involving study patients.
  - Duration: 30 to 45 minutes per interventionist.
  - Trainer: Clinical Field Specialist of the sponsor

Validation: the trainer will assess if the medical doctor who will be involved in the study procedure involving study patients has understood the theoretical training and is comfortable with the manipulation of the study device. 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.
    - 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: medical doctor doing the procedure.
  - Duration: duration of preparation and the recanalization treatment of the leg.
  - 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 (optional)
  - 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 treatment in case the treating physician has questions.

Validation:

During Step 3 and/or 4, the trainer will assess if the medical doctor (who will be involved in the study procedure) 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.

17.2 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.

17.3 Sponsor's responsibilities

The sponsor of this study is responsible for the following:

- Select the clinical investigators
- Obtain approval to begin the study, if required
- Develop 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
- Develop and/or get the approval of an adequate informed consent form
- Ensure training on the study device and study procedure
- 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)

17.4 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.

18 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.

18.1 Monitoring procedures

The sponsor and/or their designee will oversee the progress of this clinical investigation 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 remote 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 investigational 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.

18.2 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.

19 Ethical consideration and regulatory standards

19.1 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.

19.2 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.

19.3 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.

19.4 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.

19.5 Liability coverage

Subject indemnification and insurance will be purchased adhering to the applicable European requirements.

19.6 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.

20 Confidentiality of data

All information and data sent to parties involved in study conduct concerning patients or their participation in this study will be considered confidential per the requirements of the EU GDPR regulations, the MDR and other regulations per local requirements.

The Informed Consent shall describe the process of subject data protection in full. Each enrolled subject will be assigned to a unique study ID number, which is pre-configured in the EDC. Records of the subject/study ID number relationship will be maintained by the study center at a locked location where study staff only has access to. The study ID number is to be recorded on all study documents to link them to the subject's medical records at the site.

To maintain confidentiality, the subjects' name or any other personal identifiers should not be recorded on any study document other than the Informed Consent Form. In the event a subject's name is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel.

Confidentiality of data will be observed by all parties involved, at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

21 Publications and presentations

Publications and presentations referring to this clinical investigation 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 proposes a plan for communications and publications regarding the study (primary and secondary objectives, sub analysis) and potential sub studies. The 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.

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 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 ivential, 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.

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Annexes

Annex 1 – Descriptions of changes between different CIP versions

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