Study Name	**INSPECT**
Study Title	**InvestigatioN of a Smart Probe for lung lEsion Characterization using impedance Technology**
Protocol Number	**SEN_ONCO_1**
Version	**4**
Date	**4 Juillet 2024**

CLINICAL INVESTIGATION PLAN

	Name	Function	Date/Signature
Prepared by	Lise SCHAUB	Clinical Research Coordinator	05-juil.-2024 DocuSigned by: F23DB457E765460...
Reviewed by	Julie LAFAURIE	Clinical and Preclinical Lead	05-Jul-2024 DocuSigned by: 98CCEA2E8FFE4FA...
Approved by	Alina LATUS	QA/RA Lead	05-Jul-2024 DocuSigned by: E36A3A39F7F143E...

Version	Change[1]
1	Creation
2	Adjustments for submission to French authorities. Details are presented in Annex 1.
3	Adjustments requested by French ethic committee. Details are presented in Annex 1.
4	Updated after the DSMB set-up. Details are presented in Annex 1.

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 pulmology. Moreover, this CIP is conformed to the applicable regulatory guidelines, including the Declaration of Helsinki (October 2013), the MDR 2017/745, the ISO 14155 (2020) and the applicable regulatory authority requirements of the countries in which this clinical investigation will take place.

Signature and date:
Alina LATUS
Quality Assurance and Regulatory Affairs

Signature and date:
Julie LAFAURIE
Clinical & Preclinical Lead

Signature and date:
Dr. Amir HANNA
Coordinating Investigator

2 Statement of compliance

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

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

Principal Investigator's Name: _____

Site Name: _____

Principal Investigator's Signature: _____

Date of signature: _____

3 Study contacts

Function	Name	Address	Contact Details
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Local Sponsor Australia	Pacific Clinical Research Group (PCRG) Pty. Limited	Pacific Clinical Research Group TM Pty Ltd Level 36, 1 Macquarie Place Sydney, NSW, 2000 AUSTRALIA	[redacted]

4 List of abbreviations

Term	Definition
ADE	Adverse Device Effect
AE	Adverse event
BLE	Bluetooth Low Energy
BSS	BioSpy System
CA	Competent Authorities
CBCT	Cone Beam CT scan
CIP	Clinical Investigation Plan
CSGS	Clotild® Smart Guidewire System
CT scan	Computed Tomography Scan
DSMB	Data Safety Monitoring Board
EBUS	EndoBronchial UltraSound
EC	Ethics Committee
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
IB	Investigator's Brochure
ICF	Informed Consent Form
LAR	Legally Authorized Representative
MRI	Magnetic Resonance Imaging
OEM	Original Equipment Manufacturer
PET scan	Positron Emission Tomography Scan
PICF	Patient Information and Consent Form
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect

5 Study SUMMARY

Study Title and Name	**The INSPECT study** **InvestigatioN of a Smart Probe for lung lEsion Characterization using impedance Technology**
Protocol Number	SEN_ONCO_1
Study Device	The BioSpy System (BSS), adapted from Clotild® Smart Guidewire System (CSGS)
Purpose	The objective of the study is to evaluate the feasibility of the BioSpy System (BSS) sensor to differentiate tissues that are encountered during bronchoscopic biopsy of endobronchial tumors and peripheral lung nodules and masses. The evaluation will be performed at 3 different levels: i) the ability of the system to record measurements in the lesion; ii) the ability of the system to differentiate the lesion from healthy tissue; and iii) the ability of the system to differentiate various lesion types. Safety evaluation of the clinical investigation will be carried out on an ongoing basis throughout the study.
Study type	Feasibility study (First-In-Human)
Study design	Prospective, Single-arm, Multi-center study
Number of patients and Clinical Sites	Up to 30 treated patients at two centers: one center in Australia (up to 15 patients) and one center in France (up to 15 patients).
Patient Population	Subjects presenting for bronchoscopic biopsy of lesions suspicious for lung cancer. 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 BioSpy System to acquire electrophysiological measurements in the relevant tissues during bronchoscopic biopsy.

	This endpoint represents the procedural success rate being defined as the BioSpy System obtaining at least one non-anomalous impedance measurement in the lesion during the procedure. **Secondary Endpoints** 1. The ability of BioSpy System to differentiate the lesion (nodule or mass) from healthy tissue (bronchial tissue, lung parenchyma, …). The impedance measurements of BSS will be compared to the physician's assessment based on available imaging (visual control, ultrasound, fluoroscopy etc…) 2. The ability of BioSpy System to differentiate various lesion types such as, but not limited to: • Tumoral tissue • Inflamed tissue • Necrotic tissue • Fibrosis The impedance measurements of BSS in the lesion will be compared to the histopathology analysis of the collected tissue during the biopsy.
Eligibility criteria	**Inclusion criteria** Candidates for the study must meet the following inclusion criteria below: 1. Age > 18 years

	2. Subjects with lesions eligible for lung biopsy under general anesthesia. 3. Lesion localization: a. Central or proximal lesions ≥ 10 mm in diameter confirmed by imaging (CT scan and/or PET scan) and/or endobronchial visual control; or b. Peripheral lesions ≥ 20 mm in diameter confirmed by imaging (CT scan and/or PET scan) and/or ultrasound analysis (RP EBUS with central localization of the ultrasound probe) during the procedure. 4. 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 lesion <10 mm for central and <20 mm for peripheral lesions (as determined on previous imaging) 2. Contra-indication to bronchoscopy procedures 3. Contra-indication to general anesthesia 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)
Study Procedure	The physician will access the lesion as per routine practice with a bronchoscope and a commercially available biopsy needle. After study device preparation according to the instructions for use, measurements will be performed on the lesion and surrounding tissue such as inflamed tissue, healthy tissue (bronchial wall, lung parenchyma, etc) or mucus. At least one measurement in the lesion is to be recorded, preferably more (up to 10). The BioSpy probe is to be used in conjunction with a 21G commercially available biopsy needle (not provided).

	As much as possible, the location of the sensor shall be confirmed prior to the measurement by the available imaging: visual control by the bronchoscope, ultrasound probe, fluoroscopy, CBCT etc. Available imaging during the procedure will be collected by the sponsor (for example X-ray fluoroscopy recorded in real time during the use of the BioSpy probe). Tissue collection (biopsy) will be performed as per routine biopsy protocol. Ex-tempo analysis (ROSE – Rapid On Site Evaluation) might be performed if possible at the clinical center. Histopathology analysis will be performed as per hospital's routine. Images of scanned slices (histology, cytology, etc.) and analysis reports will be collected. In order to compare analysis among various centers, an analysis grid (worksheet) will be created at the start of the study and will be filled by the local histopathology laboratory. Previous or additional imaging (CT, PET/CT, other) performed during the diagnosis process might be collected to complement the analysis of the lesion (suspicion of necrotic core, vascular cells, etc.)
Estimated Study Duration and Timelines	**<u>Total study duration:</u>** Up to 9 months enrolment period per site Australia: 25 Mar 2024 – 24 Dec 2024 France: 1 Sep 2024 – 31 May 2025 **<u>Follow-up duration:</u>** Per patient: Until discharge up to 12 hrs (+/- 4hrs) post-procedure

6 Introduction

6.1 Purpose of the study

The objective of the study is to evaluate the feasibility of the BioSpy System (BSS) sensor to differentiate tissues that are encountered during bronchoscopic biopsy of endobronchial tumors and peripheral lung nodules and masses. The evaluation will be performed at 3 different levels: i) the ability of the system to record measurements in the lesion; ii) the ability of the system to differentiate the lesion from healthy tissue; and iii) the ability of the system to differentiate various lesion types.

As the BSS is not intended to be CE-marked in its current design, no safety endpoint will be measured in this clinical investigation. However, safety data will be collected and analyzed throughout the study according to the Good Clinical Practice ISO 14155:2020 (see section 16) and will be described in the final Clinical Study Report.

6.2 Scope and burden of disease

Lung cancer is the most lethal cancer worldwide with 1,8 millions of deaths per year and 2,2 million new cases (Sung et al. 2021).

Diagnosis at an early stage of the lung cancer (stage I or II) improves survival by a factor of 9 compared with a later diagnosis (IV) ((Horeweg et al. 2013),(Goldstraw et al. 2016)). The initial biopsy, which involves removing a fragment of tissue for microscopic examination, is therefore critical to confirm the diagnosis as early as possible. A failed or falsely negative biopsy can delay diagnosis for up to 6 months, even though progression can be as rapid as +32% in 8 weeks (Soukiasian Harmik et al 2018). In addition, the cost of treatment increases by a factor of 3 between stage I ($7k/month) and stage IV ($21k/month) (Gildea et al. 2017).

6.3 Clinical presentation and lung cancer biopsy

Given the importance of biopsies in the decision and treatment of lung cancer, several technologies have been developed and investigated to improve the quality of lung cancer biopsy and its diagnostic yield in peripheral lung regions. Nevertheless, the two most commonly used procedures remain endobronchial biopsy (Figure 1, top) using an ultrasound probe, the radial E-BUS (EndoBronchial UltraSound), and transthoracic biopsy (Figure 1, bottom).

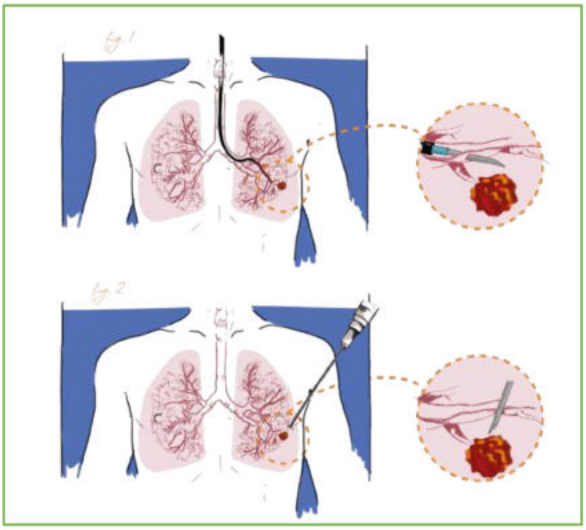


Figure 1: Most commonly used biopsy methods. Top: Endobronchial biopsy – Bottom: Transthoracic biopsy

In peripheral endobronchial biopsy, a bronchoscope is first inserted into the airways but has a certain limit, as its diameter might not be able to reach the peripheral part. A catheter with the radial-EBUS (EndoBronchial UltraSound) probe is then introduced into the airways through the bronchoscope that is in place, in order to locate the lesion by ultrasound imaging in the more distant (peripheral) airways.

Once the lesion has been located, the catheter is left in place, and the radial EBUS probe is replaced by the biopsy needle to complete the tissue sampling. Unfortunately, when removing the radial EBUS to insert the biopsy needle, the manipulation hereof might move the catheter relative to the lesion. Also due to the patient's breathing, the interventional pulmologist is forced to perform a 'blind sampling' as he/she cannot be sure of the exact location of the lesion. The diagnostic yield of forceps biopsy is documented to about 72% (Sryma et al. 2021).

Transthoracic biopsy involves guiding a needle through the lung from the outside under CT scan. This procedure has a higher diagnostic yield (around 90%) but carries a significant risk of pneumothorax in 1 out of 4 cases (Horeweg et al. 2013).

Other technologies based on imaging, e.g. Cone beam CT, fluoroscopy, confocal mini-probe (Mauna Kea Technologies), electromagnetic technology (ENB), or new robotic platforms (e.g. Ion or Monarch) that allow more precise procedural gestures, are also being used or are under clinical investigation to improve the yield of the endobronchial approach. Nevertheless, by combining the various biopsy techniques with an endobronchial approach, the diagnostic yield of peripheral lung lesions can vary between 42% and 85% (Ishiwata et al. 2019). Only histological examination after the procedure will reveal whether the tissue removed was relevant and whether the examination is conclusive. If not, a new biopsy procedure for the same patient must be scheduled, with delays in diagnosis and treatment that may increase the risk of mortality for the patient. This risk of delay is now a major concern for pulmologists and the development of a product capable of improving endobronchial diagnostic yield is eagerly awaited, as they see these delays as a loss of chances for the patient.

6.4 Benchmark of comparable devices

[redacted]

6.5 Rationale and evidence for Investigational Procedure/device

The technological solution developed by SENSOME aims to overcome these drawbacks by using an electrical impedance sensor capable of identifying the nature of the tissue to be biopsied (e.g. cancerous or non-cancerous) using machine learning models.

The SENSOME technology stands out from the above-mentioned solutions for two main reasons:

1. Its degree of miniaturisation, making it possible to develop a tool that will be perfectly integrated into the existing workflow;
2. Real-time analysis based on impedance signals with a high degree of precision.

The first medical device developed by SENSOME was Clotild® Smart Guidewire System (CSGS), a neurovascular guidewire. The CSGS is currently under investigation in the CLOT OUT study

(NCT04993079) in acute ischemic stroke interventions where the biological nature of the occlusion (caused by clot) is assessed. SENSOME's goal is to provide treating physicians with information on the nature of the clot which could help them making an informed choice on the most effective strategy for future mechanical thrombectomy.

With the development of its first product in the neurovascular field, SENSOME has already achieved significant technological development and manufacturing experience. SENSOME's second device, derived from CSGS, is a 0.014'' (0.36 mm) diameter probe to be placed inside a biopsy needle once the obstructing stylet has been removed. Its name is BioSpy System (BSS) and it is indicated for lung masses diagnosis during bronchoscopic biopsy procedure. The BioSpy probe brings the tissue sensor in contact with pulmonary tissues. SENSOME aims to provide in real time the operator with information regarding the nature of the pulmonary tissue, allowing in the future the confirmation of the position of the needle before the tissue is removed for histopathological analysis. This could lead to an improvement of diagnostic yield of bronchoscopic biopsies, combining the advantage of an endobronchial approach (safer procedure) with a diagnostic yield comparable to that of transthoracic biopsy (>90%).

Currently, biopsy needles are already fitted with a metal stylet to prevent biological material from entering the needle during navigation in the pulmonary tissues. The BioSpy probe will be inserted into a commercially available needle and will not interfere with the current workflow of a biopsy performed by the interventional pulmologist.

The objective of the INSPECT study is to evaluate the feasibility of the BioSpy System sensor to differentiate tissues that are encountered during bronchoscopic biopsy of endobronchial tumors and peripheral lung nodules and masses. To explore as many types of tissues as possible, both central and peripheral lesions will be measured, although the clinical benefit of SENSOME's technology will probably be more important for peripheral lesions that are less accessible that the central ones.

7 Identification and description of the investigational device

7.1 General description of the investigational device and its components

The BioSpy probe measures 195 cm in length and 0,014" in diameter. It is equipped, at its distal tip, with a miniaturized sensor the measurement of electrophysiological characteristics of the surrounding tissue.

The complete BioSpy System is composed of two main sub-systems (Figure 2):

- The BioSpy probe (1) with its transmitter (2) and accessories: a stopper, also called torquer (3) and a blunt insertion needle (4). All these parts are sterile and for single use only.
- The user interface that is provided via a dedicated medical tablet (5) that is equipped with a BLE dongle (6) to communicate with the transmitter. A proprietary Cloviz® application runs on the tablet to ensure interaction with the sensor, signal processing, and data storage.

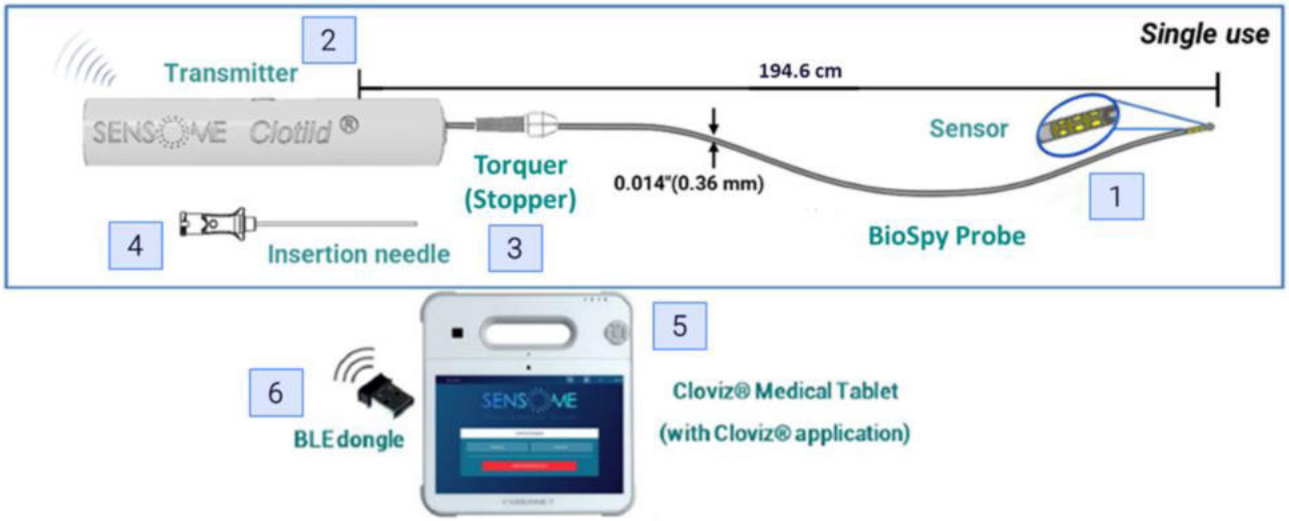


Figure 2: BioSpy System overview.

All the intelligence of the BioSpy probe is concentrated in the sensor area. The sensor is composed of 3 rows of electrodes with 3 electrodes per row, totalling 9 electrodes (Figure 3). 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**'.

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

The BioSpy probe is to be placed inside a biopsy needle (not provided) once the obstructing stylet has been removed (Figure 4). The BioSpy probe is intended to be used with existing catheters and 21G biopsy needles with straight entry. The Figure 4 shows the setup with BioSpy inserted into the biopsy needle once the obstructing stylet has been removed. The transmitter is connected to the probe's proximal connector rings.

Figure 4: Set Up of the BioSpy System inserted in a commercially available biopsy needle.

All the interactions with the probe's sensor are performed through the touchscreen medical tablet carrying proprietary application Cloviz® software (Figure 5). The tablet is supplied with a Bluetooth USB

dongle that provides wireless communication with the transmitter. [redacted] In the context of this study, the user is invited to position the sensor at the relevant locations and record measurements. 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 BioSpy System has no effect on the biopsy procedure, the user not being able to modify his/her choice of treatment based on the BSS display.

Figure 5: Medical Tablet with Cloviz® Software.

7.2 Regulatory classification

The BioSpy System (BSS) meets the criteria for a Medical Device (Article 2, 2017/745[2]) and it belongs to Class IIa medical device according to Rule 5[3] and Rule 11[4] of the Medical Device Regulation (2017/745), as described Annex VIII, and the MDCG endorsed document MDCG-2021-246.

[2] as amended by regulation (EU) 2020/561 of the European Parliament and of the Council of 23 April 2020.
[3] Rule 5 = all invasive devices with respect to body orifices, other than surgically invasive devices, intended for connection to a class IIa, class IIb or class III active device, are classified as class IIa.
[4] Rule 11 = software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa.

Cloviz® software is a Class B[5] software according to IEC 62304.

7.3 Intended purpose and indication

Intended use

The BioSpy System is intended to allow measuring electrophysiological parameters of pulmonary tissues during bronchoscopic biopsy procedure.

Indication of use

BioSpy System is indicated for lung masses diagnosis.

7.4 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 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:

[5] "The software system can contribute to a hazardous situation which results in unacceptable risk after consideration of risk control measures external to the software system and the resulting possible harm is non-serious injury" according to IEC 62304:2006/AMD1:2015.

- 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.

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.

7.5 Pre-clinical testing

In order to provide evidence that the device under study is sufficiently safe and performant for early human experience, pre-clinical testing was performed to evaluate:

- Biological safety
- Mechanical safety
- Electrical safety
- Sterility
- Mechanical performance
- Electrical performance
- Software validation
- Usability

All tests are extensively detailed in the Investigator's Brochure (*CLI_INVEST_BROCH_BSS_INSPECT_V2* and later version). Amongst those tests, 2 major experiments can be described in this document: a

simulative use performed using a non-living swine model and an ex-vivo research program performed using human tissues collected during surgery. These two projects are described below.

7.5.1 Simulative use

Figure 6: Set up of BioSpy System during the simulative use.

During this test, no mechanical damage occurred and all BioSpy probes were electrically functional. Physician gave positive feedback on integrating the investigational device into standard practice. Thus, it can be concluded that this test was a success and that the BSS is suitable for a first-in-human clinical study.

7.5.2 Preliminary research program to distinguish tumoral and healthy pulmonary tissues

These results are very encouraging and show that the BioSpy probe has great capacities of tissue distinction, comforting the idea that the INSPECT study might be a success.

8 Study Design and Population

8.1 Study design

This study is a prospective multi-centre, single-arm study to evaluate the feasibility of the BioSpy System (BSS) sensor to differentiate tissues that are encountered during bronchoscopic biopsy of endobronchial tumors and peripheral lung nodules and masses.

Up to 30 treated subjects, presenting for bronchoscopic biopsy of lesions suspicious for lung cancer, will be enrolled.

Patients will be enrolled at one center in France (up to 15 patients) and one center in Australia (up to 15 patients).

The enrolment period will be approximately 9 months per site.

Analysis of the data will take place on a continuous basis and will determine the to-be-enrolled number of patients. Subjects will be selected as per the inclusion/exclusion criteria of the protocol.

All bronchoscopic biopsy procedures will be done using devices (commercially available or devices under research, after written approval of SENSOME) as per their IFU and using the BioSpy System.

8.2 Eligibility criteria

8.2.1 Inclusion criteria

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

1. Age > 18 years
2. Subjects with lesions eligible for lung biopsy under general anesthesia.
3. Lesion localization:
    a. Central or proximal lesions ≥ 10 mm in diameter confirmed by imaging (CT scan and/or PET scan) and/or endobronchial visual control; or
    b. Peripheral lesions ≥ 20 mm in diameter confirmed by imaging (CT scan and/or PET scan) and/or ultrasound analysis (RP EBUS with central localization of the ultrasound probe) during the procedure.
4. Written Informed Consent to participate in the study.

8.2.2 Exclusion criteria

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

1. Target lesion <10 mm for central and <20 mm for peripheral lesions (as determined on previous imaging)
2. Contra-indication to bronchoscopy procedures
3. Contra-indication to general anesthesia
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)

9 Study Objectives

9.1 Primary objective

The ability of BioSpy System to acquire electrophysiological measurements in the relevant tissues during bronchoscopic endobronchial lung biopsy.

This endpoint represents the procedural success rate being defined as the BioSpy System obtaining at least one non-anomalous impedance measurement in the lesion during the procedure.

9.2 Secondary objective

The secondary objective of the study is to evaluate the performance of BSS, defined here as the feasibility to differentiate the lesion from healthy tissue. Also, to evaluate if the BSS can differentiate different types of lesions.

10 Study Endpoints

10.1Primary Endpoints

The ability of BioSpy System to acquire electrophysiological measurements in the relevant tissues during bronchoscopic biopsy.

This endpoint represents the procedural success rate being defined as the BioSpy System obtaining at least one non-anomalous impedance measurement in the lesion during the procedure.

10.2Secondary Endpoints

1. The ability of BioSpy Sysem to differentiate the lesion (nodule or mass) from healthy tissue (bronchial tissue, lung parenchyma, …). The impedance measurements of BSS will be compared to the physician's assessment based on available imaging (visual control, ultrasound, fluoroscopy etc…)
2. The ability of BioSpy Sysem to differentiate various lesion types such as, but not limited to:

   - Tumoral tissue
   - Inflamed tissue
   - Necrotic tissue

- Fibrosis

The impedance measurements of BSS in the lesion will be compared to the histopathology analysis of the collected tissue during the biopsy.

11 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 BSS 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.

11.1 Risk minimization

11.1.1 Pre-clinical risk minimization

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

Residual risks have been categorized in the following categories: I (unacceptable); II (undesirable); IIIA (less tolerable); IIIB (tolerable) and IV (acceptable).

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 assessment by experts in the field 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_BSS_V2* 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_BSS_V2* or later version) and comes from the risk analysis.

11.1.2 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 bronchoscopic lung biopsies.
- Sufficient level of clinical expertise and support to manage adverse events that could arise and are able to provide appropriate alternative therapies if required.
- The sponsor has clearly defined inclusion and exclusion criteria and will assign monitors to verify compliance to these, to ensure that only appropriate subjects are enrolled.
- An extended training will be provided highlighting the differences between (the use of) the BioSpy System (BSS) and commercially available diagnostic probes. Please refer to section 17.1.2 Necessary training and experience for more details on the provided training.

11.1.3 Risk minimization during the study

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

- The investigator will obtain informed consent from each subject 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.
- 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 and regulations 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.

11.1.4 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be set-up:

- Consisting out of an expert in the field. 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 DSMB charter.

11.2 Risks associated with participation in the clinical investigation

Anticipated AEs and ADEs were identified through the risk analysis. Information regarding known or foreseeable risks, any undesirable effects, contraindications and warnings are detailed in the Instructions For Use (*DND_IFU_BSS_V2* or later version) and comes from the risk analysis.

During use of the BioSpy System, adverse events may occur, including but may not be limited to the following:

- Cardiac arrest,
- Respiratory distress,
- Air embolism,
- Allergic reaction,
- Hemoptysis,
- Pneumothorax,
- Hemomediastinum,
- Hemothorax,

- Nerve injuries,
- Organ or vessel perforation or injury,
- Foreign body non-vascular,
- Pseudoaneurysm,
- Pulmonary infarction,
- Dysphagia,
- Dysphonia,
- Vasovagal reaction,
- Hypotension / hypertension,
- Chest pain.

11.3Benefit vs Risk Assessment

BSS has been designed to identify the nature of lesion composition in situ and in real time during intervention. In the future BSS might provide physicians with information on the nature of the lesion that will be sampled for biopsy, which will help to precise sampling location for future bronchoscopic biopsies.

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 and or sequence of devices to be used in the bronchoscopic biopsy. Upon completion of the study, data collected may benefit the future patients at large, through helping physicians to choose the most effective strategy for biopsies.

The expected benefits of the BSS outweigh the potential risks associated with its expected use. Through the BSS 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 review process. The materials and manufacturing processes of BSS 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.

12 Study Visit Assessments

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

12.1Informed Consent and Revision

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

12.2Informed 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 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 patient's eligibility for the study will be assessed by the investigator. If the patient is eligible, the investigator will do their due diligence to explain the study (and study procedure) and the associated risks and benefits of participating to the patient and/or their family members. The patient or their family will be encouraged to ask questions regarding the study to aid them in the subject's decision to voluntarily participate in the study. The investigator will allow the participant time to consider their

participation and discuss with their family members. The investigator will emphasise to the patient that participation in the study is voluntary. This means they do not have to take part, and that he/she may discontinue their involvement at any time without penalty or loss of benefits to which they are otherwise entitled.

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 study procedure.

12.3Point 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.

12.4Treated patients

A treated patient is a patient in whom the BioSpy System went through the bronchoscope.

12.5Procedural success

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

12.6Screen Failures

Patient having signed the informed consent form but however whose eligibility could not be (re)confirmed on the day of the study procedure is being considered as a screen failure.

Only screening assessments will be collected and entered in the eCRF.

12.7Schedule 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.

Clinical investigation plan – INSPECT study

The schedule of events is the same for all subjects in the trial. All subjects who are enrolled into the trial will be followed for 12 hours (+/- 4hrs) post-study procedure or at discharge (what comes first). Please refer to table 2 for the schedule of the assessments required.

Table 1: Schedule of Assessments.

Parameter/Examination	Screening/Baseline	Bronchoscopic procedure	12 hrs (+/- 4hrs) post study procedure or Discharge *****
Inclusion/Exclusion criteria	X		
Demographics & Medical History incl.	X		
Pregnancy test*	X		
Vital Signs (as per hospital normal practice)	X	X	
Patient Information/ informed consent	X		
Imaging exams	PET scan / CT scan / MRI **	CT scan / fluoroscopy**	
Biopsy procedure (number, location, biopsy medical device, ROSE outcome, …)		X	
Histopathology analysis of the biopsy samples***		X	
AE/SAE****		X	X

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

** PET scan / CT scan / MRI / fluoroscopy acquired as per normal hospital practice will be collected

*** Images of scanned slices (histology, cytology etc) and analysis reports will be collected.

**** In case of (S)AE, supporting information may be collected via the AE CRF, such as concomitant medication, lab values, vital signs.

***** Patients will be followed at 12hrs (+/- 4hrs) post procedure or discharge (what comes first)

12.8Screening/Baseline visit

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

- Confirmation that all inclusion and none of the exclusion criteria have been met
- Informed consent
- Demographics (Year of Birth, gender)
- Medical history (incl. lung tumor specifics)
- Pregnancy test according to site specific standard of care (e.g. test, verbal communication)
- Vital Signs (as per normal hospital practice - screening only)

Medical Imaging will be according to the hospital practice. This can be PET scan, CT scan , MRI or any other medical imaging technique used to locate the lesion suspected of being a lung tumor. Subject's evaluation will be performed in accordance with the standard of care at the participating sites.

12.9Lung Biopsy procedure

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

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

- Time of insertion of bronchoscope
- Time of study procedure (and end of study procedure)
- Time of first and last biopsy
- Time of removal bronchoscope

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

12.10 Study procedure

The physicians will access the lesion as per routine practice with a bronchoscope and a biopsy needle of choice.

After study device preparation according to the instructions for use, measurements will be performed on the lesion and surrounding tissue such as inflamed tissue, healthy tissue (bronchial wall, lung parenchyma, etc) or mucus.

At least one measurement in the lesion is to be recorded, preferably more (up to 10). The BioSpy probe is to be used in conjunction with a 21G commercially available biopsy needle (not provided) with straight entry.

As much as possible, the location of the sensor shall be confirmed prior to the measurement by the available imaging: visual control by the bronchoscope, ultrasound probe, fluoroscopy, CBCT etc.

The study procedure ends with the final removal of the BioSpy System from the bronchoscope.

A total number of 1 (one) to 2 (two) investigational devices is expected to be used per patient.

Note that the study procedure includes the manipulation of the BSS, from the tablet preparation to removal of the study device from the bronchoscope.

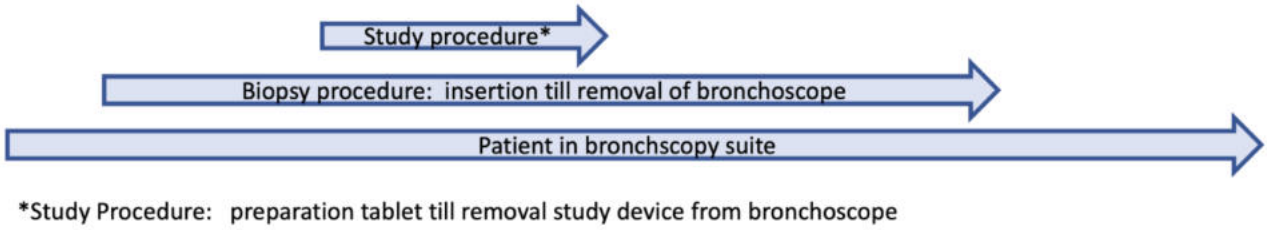


Figure 7: Schematic explaining how the study procedure is structured within the bronchoscopy procedure.

A Treated patient is a patient in whom the BioSpy System went through the bronchoscope.

Available imaging during the procedure will be collected by the sponsor (for example X-ray fluoroscopy recorded in real time during the use of the BioSpy probe).

Tissue collection (biopsy) will be performed as per routine biopsy protocol.

Ex-tempo analysis (ROSE – Rapid On Site Evaluation) might be performed if possible at the clinical center.

Histopathology analysis will be performed as per hospital's routine. Images of scanned slices (histology, cytology etc) and analysis reports will be collected. In order to compare analysis amongst various centers, an analysis grid (worksheet) will be created at the start of the study and will be filled by the local histopathology laboratory.

Previous or additional imaging (CT scan, PET scan, MRI, …) performed during the diagnosis process might be collected to complement the analysis of the lesion (suspicion of necrotic core, vascular cells…).

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

- Collection of the BSS, which will then be sent to SENSOME for physical inspection.
- CT scan / MRI / fluoroscopy if available per local hospital practice will be collected by sponsor.

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

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

12.11 Follow-Up - 12 hours (range 8-16hrs) post-procedure or Discharge

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

The following data will be collected:

- New Adverse Events and Serious Adverse Events until 12 hrs (+/- 4hrs) post procedure or until discharge (what comes first)

For all subjects that decease prior to the follow-up assessment, available information regarding the primary cause of death and date/time of death will be recorded.

12.12 Management of patients at the end of the study

Patient management beyond the participation in this study should be done 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.

13 Study Handling Procedures

13.1Return of used BioSpy System to sponsor

Used BioSpy probes will be washed with saline solution, rolled up and stored in a biohazard plastic bag (provided by the sponsor) with device number indicated. BioSpy transmitter will be stored in a separate biohazard plastig bag.

Devices will be stored before shipment to SENSOME for physical inspection.

An operation manual will provide detailed information on the handling and processing of the used devices which will also be summarized in section 7.4.

14 Statistical consideration

This is a multi-centre, non-randomized, prospective, feasibility study designed to evaluate the feasibility of the BioSpy System sensor to differentiate tissues involved in subjects with lung tumors.

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

14.1Statistical Analyses

In this study, the user is invited to record impedance measurements at various relevant locations during a bronchoscopic biopsy 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 this study cannot be displayed to the physician during the study.

As a consequence, the use of the BioSpy System has no effect on the bronchoscopic procedure, the user not being able to modify his/her choice of treatment based on the BSS display. For this reason, the design of the study does not include randomization or control group or blinded arm.

Due to the feasibility 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 this purpose and will be used to develop statistical models to differentiate tissues.

14.2Analyses population

At most 30 subjects with lesions suspicious for lung cancer will be enrolled in two sites for this study.

Intention To Treat (ITT) Population

All patients who were enrolled, so all patients who signed and dated the patient information consent form even though the BioSpy System was not used in the subject.

Treated Population

All patients in which the BioSpy System went through the bronchoscope. 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 BioSpy System will be used. The evaluation of tissue differentiation capabilities (see secondary endpoints) will be performed on this population set.

14.3Endpoint analysis

14.3.1Primary Endpoint analysis

For the **Primary Endpoint** descriptive statistics will be provided showing the proportion of patients in which at least one non-anomalous impedance measurement in the relevant tissues could be obtained.

The primary endpoint is the ability of BioSpy System (BSS) to acquire electrophysiological measurements in and around the lesion. 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 3). This endpoint represents the procedural success rate - procedural success being defined as the BSS obtaining at least one non-anomalous impedance measurement in and around the lesion during the bronchoscopic procedure. Given the feasibility nature of the study, a success rate of 60% is expected.

Data coverage will be calculated.

14.3.2Secondary Endpoint analysis

1) The ability of the BioSpy System to differentiate the lesion (nodule or mass) from healthy tissue (bronchial wall, parenchyma, …). The impedance measurements of BSS will be compared to the physician's assessment based on available imaging (visual control, ultrasound, fluoroscopy etc…

2) The ability of the BioSpy System to differentiate various lesion types such as, but not limited to:

   - Tumoral tissue
   - Inflamed tissue
   - Necrotic tissue
   - Fibrosis

The impedance measurements of BSS in the lesion will be compared to the histopathology analysis of the collected tissue during the biopsy.

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

To further assess the secondary endpoints, 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).

14.4Sensitivity analysis

The need for sensitivity analyses will be explored during the conduct of the study.

14.5Study 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 3) and the possibility to collect multiple measurement points during the procedure (see section 12.10). Previous experience in prediction model development showed that a sample size of maximally 30 subjects will be enough to evaluate the feasibility of the sensor to differentiate tissues.

14.6Missing 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 BSS, 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 needle 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.

14.7Bias

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 expert in the field. 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

15.1Ethical 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.

15.2Amendments

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 model. Information obtained from these other projects (thus increasing understanding) may trigger the need to amend this Clinical Investigation Plan.

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

An overview of the previous versions will be listed. Documentation of changes can be found in annex of this document 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.

15.3Data management

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

The eCRF will contain a record of the subject's eligibility to enter the study, relevant medical history, pre-procedure assessments, concomitant medications, a record of all investigational products used during the procedure, all procedural complications and adverse events, as well as discharge, follow up, and any unscheduled visits.

The investigator must sign and date the specified section of the 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 CRFs 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 organization 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
- Evidence of Patient Information Letters that have been sent to the patients; Patients signed ICFs (if required with study number and title) or Patient Information Letters where refusal of participation has been indicated
- Any other pertinent study document.

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

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

15.4Source 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.

15.5Protocol 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

15.6Early 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 CRFs 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.

15.7Study termination

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

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

The investigator must implement the Sponsor's request to terminate the study in a time frame that fits with the subject's best interest.

In case of early termination of the clinical investigation the sponsor must notify the competent authority and ethics committee 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 and ethics committee 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 ethics committees and the competent authority by the sponsor or, in the case of an early termination or temporary halt, within 3 months.

15.8Consequences 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.

16.2Event 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.

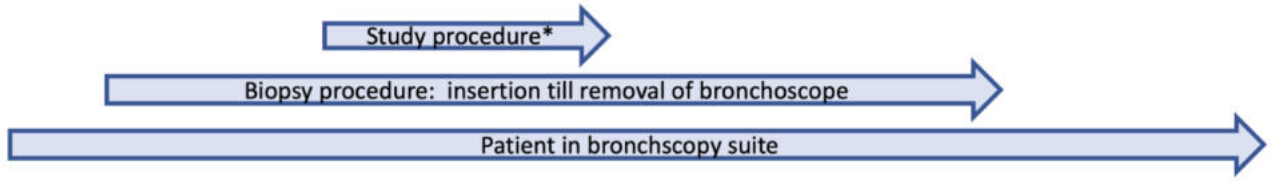
Moderate: interferes with the patient's usual activity and/or requires symptomatic treatment.

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

16.3Causality/Relationship

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

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



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

Note that the study procedure includes the manipulation of the BioSpy System, from the tablet preparation to removal study device form the bronchoscope.

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

<u>Not related:</u>

The relationship to the study device or study procedure or bronchoscopy 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 bronchoscopy 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 bronchoscopy procedure seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship:

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

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that:
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;

- the SAE follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the SAE (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable.

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

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

16.4Adverse Event Reporting

Adverse Events

Adverse Events will be collected in treated patients only, i.e. patients in whom the BioSpy System went through the bronchoscope.

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.

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

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

The Data Safety Monitoring Board (DSMB) will review all AE/SAE, as per the DSMB Charter, throughout the study.

16.5Reporting of adverse events to Ethics Committees and regulatory authorities

All device deficiencies and events related or not to the study device or the study procedure or to the bronchoscopy 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 or the investigation procedure or where such causal relationship is reasonably possible. Only "not related" events are excluded from reporting. If either the sponsor or the investigator has assigned a higher causality level than "not related", the event should be reported.

b. any DD, that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

c. any new findings in relation to any event referred to in points a) and b).

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

The sponsor shall fully record all of the following:

a) Any adverse event of a type identified in the clinical investigation plan as being critical to the evaluation of the results of that clinical investigation;

b) Any serious adverse event;

c) Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

d) Any new findings in relation to any event referred to in points (a) to (c).

Reporting must be performed:

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

b) For any other reportable event or a new finding/update to a reportable event**: immediately (but not later than 7 calendar days)** following the date of awareness by SENSOME of the new reportable event or of new information in relation with an already reported event.

The reportable events occurring in Third Countries6 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.

6 Countries other than Switzerland, Turkey and those belonging to the EEA.

16.6Device deficiencies Reporting

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.

16.7Reporting 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.

16.8Safety Analysis

Safety analysis will be performed by the sponsor together with the DSMB. The DSMB will have scheduled meetings at regular times to assess the safety in the study. A detailed DSMB charter approved by the DSMB members will clarify the methodology used by the board.

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

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

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

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

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 consent forms
- 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. This theoretical training includes pre-recorded videos about all steps.
    - Who to attend: all Interventional Pulmonologist who will be involved in the bronchoscopic procedure involving study patients.
    - Duration: 30 minutes

- Trainer: Clinical Field Specialist of the sponsor

- Step 2: Practical session
  - A practical session: hands-on session with the study device
  - Who to attend: Interventional Pulmonologist who will be involved in the bronchoscopic procedure involving study patients.
  - Duration: 30 to 45 minutes per medical doctor
  - Trainer: Clinical Field Specialist of the sponsor

  Validation: the trainer will assess if the Interventional Pulmonologist who will be involved in the bronchoscopic 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: Interventional Pulmonologist doing the bronchoscopic procedure.
  - Duration: duration of preparation and the bronchoscopy procedure involving study patients.
  - 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
  - The Clinical Field Specialist will be stand-by for the whole duration of the (preparation of) the bronchoscopy procedure in case the treating Interventional Pulmonologist has questions.

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

17.2Investigator'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.

17.3Sponsor'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 CIP, 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)

17.3.1 Financial Responsibility

This study is supported by the financial provisions of SENSOME.

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

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 are available. The sites will be monitored by monitors trained on the Clinical Investigation Plan and all study specifics to 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 convening 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.

18.2Site 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

The 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.

19.4Steering 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.

19.5Liability coverage

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

19.6Study 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 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 study will be coordinated by SENSOME to allow the use of all available data. Publications/presentations will be in adherence with the study contracts and the Publication and Presentation Charter.

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

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

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

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

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

22 References

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Annexes

Annex 1

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Clinical investigation plan – INSPECT study

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Clinical investigation plan – INSPECT study

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