AN INITIAL ASSESSMENT OF SAFETY AND PERFORMANCE OF THE SPHERE-9™ ABLATION CATHETER AND SYSTEM FOR MAPPING AND ABLATION OF ATRIAL ARRHYTHMIAS

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SPONSOR
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INVESTIGATOR'S AGREEMENT

I have read this Investigational Plan and agree to adhere to the requirements. I will provide copies of this Investigational Plan and all pertinent information to all site personnel involved in this study. I will discuss this material with them and ensure they are fully informed regarding the study products and the conduct of the study.

I agree to conduct the study as outlined in the Investigational Plan, in accordance with the signed clinical study agreement and to the ethical principles stated in the latest version of the Declaration of Helsinki (2013), the applicable guidelines for good clinical practices, MEDDEV 2.7/4 (Guidelines on Clinical investigations: a guide for manufacturers and notified bodies) and 2.7/3 (Clinical investigations: serious adverse event reporting), ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), or the applicable local and international regulations, whichever provide the greater protection of the individual. In addition, I agree to provide all the information requested in the Case Report Forms presented to me by the Sponsor in a manner to assure completeness, legibility and accuracy.

I also agree that all information provided to me by the Sponsor, including pre-clinical data, protocols, Case Report Forms, and any verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be relayed in confidence to the Ethics Committee.

In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than the Sponsor, the Ethics Committee, and competent authorities (if applicable). Any such submission will indicate that the material is confidential.

Principal Investigator's Name (print)

Title

Address

Signature / Date

STUDY SYNOPSIS

PROTOCOL TITLE	**An Initial Assessment of Safety and Performance of the Sphere-9™ Ablation Catheter and System for Mapping and Ablation of Atrial Arrhythmias**
INVESTIGATIONAL DEVICE	Affera Sphere-9 Ablation Catheter with Affera Mapping and Ablation System
POPULATION	Subjects aged ≥ 18 and ≤ 75 years presenting with atrial flutter (AFL), paroxysmal atrial fibrillation (AF) or persistent AF.
STUDY DESIGN	A prospective, single-arm, single center study in up to 30 patients.
STUDY OBJECTIVES	To evaluate the safety and performance of the Affera Sphere-9 Ablation Catheter and the Affera Mapping and Ablation System.
INCLUSION CRITERIA	1. Age ≥ 18 and ≤ 75 years. 2. Suitable candidate for catheter non-emergent mapping and ablation of atrial flutter or atrial fibrillation as follows: • Atrial Flutter defined as o At least one episode of typical (clockwise or counterclockwise) atrial flutter documented by EKG, 12 lead EKG, Holter or transtelephonic monitor, telemetry strip, or implanted device within 6 months prior to enrollment. **OR** • Atrial Fibrillation defined as o History of symptomatic paroxysmal and/or persistent atrial fibrillation within the past year documented by EKG **AND** o Failure of at least one class I-IV drug as evidenced by recurrent symptomatic AF, or intolerable to AAD. 3. Subject is able and willing to give informed consent. 4. Subject is able and willing, and has ample means to comply with all pre-, post- and follow-up testing requirements.
EXCLUSION CRITERIA	1. Documented left atrial thrombus or another abnormality which precludes catheter introduction. 2. Documented ejection fraction (EF) < 40%.

3. Contraindication to anticoagulation therapy (heparin, warfarin, or novel oral anticoagulant [NOAC]).
4. Unstable angina or ongoing myocardial ischemia.
5. Myocardial infarction, unstable angina, cardiac surgery or coronary intervention within 3 months of enrollment.
6. Congenital heart disease where the underlying abnormality increases the risk of the ablation.
7. Pulmonary hypertension (mean pulmonary artery pressure [mPAP] > 50 mmHg)
8. Enrollment in any other ongoing study protocol that would interfere with this study.
9. Documented severely impaired kidney function defined as Cockcroft-Gault Glomerular Filtration Rate (GFR) < 29ml/min.
10. Active gastrointestinal (GI) bleeding.
11. Active infection or sepsis.
12. Short life expectancy (< 1 year) due to illness such as cancer, pulmonary, hepatic or renal disease.
13. Significant anemia (defined as hemoglobin < 8.0 gr/dL).
14. Severe uncontrolled systemic hypertension with systolic blood pressure (SBP) > 200 mm Hg within last 30 days.
15. Severe bleeding, clotting or thrombotic disorder.
16. Uncontrolled diabetes.
17. Women who are pregnant or are not willing to use contraception for the duration of the study.
18. Severe chronic obstructive pulmonary disease (COPD; identified by a forced expiratory volume [FEV1] <1)
19. Prior stroke or TIA within the last 6 months.
20. Any other condition that, in the opinion of the investigator, poses a significant hazard to the subject if an ablation procedure was performed.

Additional exclusion criteria for AF patients only

21. Left atrial diameter of > 55 mm (parasternal view).
22. Prior atrial septal defect (ASD) or patent foramen ovale (PFO) closure with a device using a transcatheter percutaneous approach.
23. Hypertrophic cardiomyopathy defined as left ventricular (LV) septal wall thickness >1.5cm.
24. Prior ablation or surgery for atrial fibrillation.
25. NYHA Class III or IV

STUDY PROCEDURES

Screening should be completed within 30 days of index ablation procedure. Prior to screening, subjects will give informed consent. Initial screening will consist of review of relevant history including duration and frequency of arrhythmia(s), their subsequent

treatments (e.g., medications, previous ablation) and associated symptoms. If the subject passes the initial screening, remaining screening tests will be performed which include assessment of study eligibility, concomitant medications, physical exam, 12 lead EKG, transthoracic echocardiography (TTE), urine pregnancy test (women of childbearing potential only), and optional CT and/or MR imaging.

After confirmation of the absence of left atrial thrombus precluding catheter introduction, eligible subjects will undergo mapping and ablation. Esophageal evaluation, and CT and/or MR imaging may optionally be performed after treatment or during follow-up.

Subjects will be followed for 365 days after the ablation procedure to characterize safety and product performance. Note, the Day 10 visit can be conducted by telephone. Ambulatory monitoring will be conducted within the follow-up windows at Day 90, Day 180 and Day 365. Use of antiarrhythmic drugs (AADs) and other important cardiovascular drugs will be collected at every visit. Serious adverse events (AEs) will be collected starting on Day 0 through study exit.

SCHEDULE OF EXAMINATIONS

Visit 1 - Screening (within 30 days)
Visit 2 - Ablation (Day 0)
Visit 3 - Day 10 ± 3 days (telephone call)
Visit 4 - Day 90 ± 14 days
Visit 5 - Day 180 ± 30 days
Visit 6 - Day 365 ± 30 days

STUDY OUTCOMES

Safety: The primary safety outcome is the rate of the following serious adverse events (SAEs) occurring starting Day 0 and extending through the Day 10 assessment: transient ischemic attack; cerebrovascular accident; major bleeding; cardiac tamponade; pulmonary vein stenosis; severe pericarditis requiring extended hospitalization; myocardial infarction; diaphragmatic paralysis; atrio-esophageal fistula (through the Day 90 assessment); valvular damage; phrenic nerve palsy; intra-procedural device complications requiring open chest or heart surgery; vascular complications requiring surgical intervention; and death.

Device performance: The primary product performance outcome is determined during the procedure and is defined as the following:

- Catheter handling sufficient to reach reasonable intended targets, as determined by the physician:
  - catheter delivery to the desired cardiac chambers
  - manipulation of catheter

- completion of mapping procedure
- safe removal of catheter from the subject

- 3D electro-anatomical map creation and utility sufficient to aid diagnosis
- Generation of acceptable acute therapeutic RF lesions

The secondary product performance outcome is freedom from documented recurrence of the treated arrhythmia through the Day 365 post-treatment follow-up visit. In AF subjects, this includes freedom from documented AF, atrial tachycardia (AT), or AFL.

ANALYSIS

Descriptive statistics (N, mean, median, SD, minimum and maximum values for continuous variables, and the number and percentage of subjects in each category for categorical variables, where applicable) will be used to characterize study outcomes and safety parameters.

The Schedules of Evaluations and Visits are located in Appendix 1.

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ABBREVIATIONS

AAD	Antiarrhythmic Drug
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial Flutter
ASD	Atrial Septal Defect
β-HCG	Beta Human Chorionic Gonadotropin
CBC	Complete Blood Count
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine Phosphokinase
CRF	Case Report Form
CRO	Clinical Research Organization
CS	Clinically Significant
CT	Computed Tomography
CVA	Cerebrovascular Accident
EC	Ethics Committee
EF	Ejection Fraction
EKG	Electrocardiogram
EGM	Electrogram
FDA	Food and Drug Administration
FEV	Forced Expiratory Volume
GCP	Good Clinical Practices
GFR	Glomerular Filtration Rate
GI	Gastro-Intestinal
Hgb	Hemoglobin
HCT	Hematocrit
HEENT	Head, Eyes, Ear, Nose and Throat
LV	Left Ventricular
mPAP	mean Pulmonary Artery Pressure
MR	Magnetic Resonance
NCS	Not Clinically Significant
NOAC	Novel Oral Anticoagulant
PFO	Patent Foramen Ovale
PI	Principal Investigator
QOL	Quality of Life
RBC	Red Blood Cells
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
WBC	White Blood Cells

1. INTRODUCTION

Atrial fibrillation (AF) and flutter (AFL) affect tens of millions of people worldwide. These conditions are associated with increased risk of stroke and, in the case of atrial fibrillation, mortality. Catheter ablation using radiofrequency (RF) energy has become a widely accepted treatment for these tachyarrhythmias and is considered first-line therapy in some cases [1] [2].

AF is a supraventricular tachycardia that manifests as a rapid, irregular atrial rhythm with no clearly-defined P-wave on the electrocardiogram. It affects an estimated 33 million people worldwide, and it carries significant risks. AF leads to dramatically increased risk of stroke, increased risk of heart failure, and increased mortality. Furthermore, AF is often symptomatic, leading to fatigue and reduced quality of life (QOL); however, it carries similar risks with or without symptoms [2].

The success rate of catheter ablation for atrial fibrillation is superior to the efficacy of antiarrhythmic drugs. For example, the RAAFT-2 trial found that catheter ablation led to a 55% recurrence rate for atrial fibrillation or atrial tachycardia at 2 years follow-up compared to 72% recurrence using antiarrhythmic drugs [2]. Ablation is also associated with a complication rate of 2-3% [4].

Catheter ablation is a class I recommendation for the treatment of symptomatic drug-refractory paroxysmal atrial fibrillation. Catheter ablation is considered a reasonable treatment for persistent atrial fibrillation as well as for paroxysmal atrial fibrillation prior to starting anti-arrhythmic drugs [2]. However, pulmonary vein reconnection is common, and repeat ablation is often necessary [2] [5].

Atrial flutter is a supraventricular tachycardia characterized by a rapid, organized atrial rhythm with clear P-waves on the electrocardiogram. Atrial flutter is less common than – and is usually accompanied by – atrial fibrillation [6] [2]. The incidence of atrial flutter increases rapidly with age over 50, affecting more than 5% of the population over 80 years of age, and it is significantly more common among men than women [6].

Catheter ablation of atrial flutter is usually effective, with is a small risk of recurrent atrial flutter and also a risk of atrial fibrillation during follow-up [7]. RF catheter ablation is considered a relatively safe and effective procedure for the therapeutic treatment of typical atrial flutter [8]. Catheter ablation is a class I recommendation for many symptomatic atrial flutters, particularly when pharmacological treatment has failed [1]. However, repeat procedures are sometimes required to achieve long-term success [9].

1.1. STUDY RATIONALE

The application of durable RF ablation lesions remains an unmet need in catheter ablation for atrial fibrillation and flutter [2] [5] [9]. Nondurable lesions lead to electrical reconnection in the heart and the recurrence of the arrhythmia, requiring repeated treatment, or may create new arrhythmia circuits that may be more serious [1]. The Affera Sphere-9 Ablation Catheter and Affera Mapping and Ablation System have been developed to create safe and effective lesions in the heart.

The Affera Sphere-9 ablation catheter is an irrigated 8F bidirectional cardiac ablation catheter. The catheter employs an expandable ablation electrode that is designed to safely create durable lesions. Mounted on the ablation electrode are 9 mini surface electrodes that are used for detecting localized electrograms to aid in mapping and monitoring lesion formation. The local impedance of these surface electrodes is measured to provide the user with information regarding the proximity of each electrode to the tissue. In addition, each surface electrode contains a temperature sensor for providing localized surface temperature feedback, which allows tailored power titration.

The Affera Mapping and Ablation System are designed for use with the Sphere-9 catheter. The system utilizes the added feedback information from the catheter to maximize RF delivery, and is designed to streamline the workflow of the mapping and ablation procedure. The Affera Mapping and Ablation System includes an RF generator with a user interface for controlling and monitoring energy delivery. It also includes a visualization interface for localizing the catheter, displaying electrograms, and constructing electroanatomical maps.

With the combination of catheter handling, controlled lesion formation, and proximity and temperature feedback, the Sphere-9 Ablation Catheter and Affera Mapping and Ablation System are anticipated to safely and effectively treat a variety of arrhythmias.

2. DEVICE DESCRIPTION

2.1. AFFERA SPHERE-9 ABLATION CATHETER

The Sphere-9 Ablation Catheter is a sterile, single-use 8F deflectable cardiac ablation and mapping catheter. The Sphere-9 Ablation Catheter employs similar technology as commercially available cardiac ablation catheters, including catheter shaft materials, steering mechanism, location sensor, electrogram electrodes and irrigation. The catheter features a unique expandable ablation electrode that provides a larger effective surface area for delivery of RF energy and allows for the placement of multiple discrete mini surface electrodes for collection of more localized electrogram and local impedance information than conventional ablation catheters. Each surface electrode also contains a discrete temperature sensor, providing more localized temperature feedback than conventional ablation catheters.

The catheter consists of a handle to control bidirectional deflection of the 7.5Fr steerable shaft. The ablation electrode on the tip of the catheter expands to 9mm in diameter when deployed and collapses for introduction through an 8Fr introducer sheath. Nine mini surface electrodes are mounted on the expandable ablation electrode and are spaced 5mm apart for recording highly localized electrograms. Each surface electrode is driven with a sensing current by the Mapping System in order to determine its Local Electrode Impedance, which can provide information to

the user regarding the proximity and orientation of the tip to the cardiac tissue. Each surface electrode also contains a temperature sensor that reports localized temperature to the RF Generator. The catheter contains an irrigation lumen that connects via a standard luer connector to irrigation solution (heparinized saline) provided by an irrigation pump and tubing set. Irrigation provided from within the expandable ablation electrode reduces the likelihood of thrombus and coagulation. The catheter also contains passive electromagnetic location sensors in the tip and shaft to allow localization by the Mapping System.

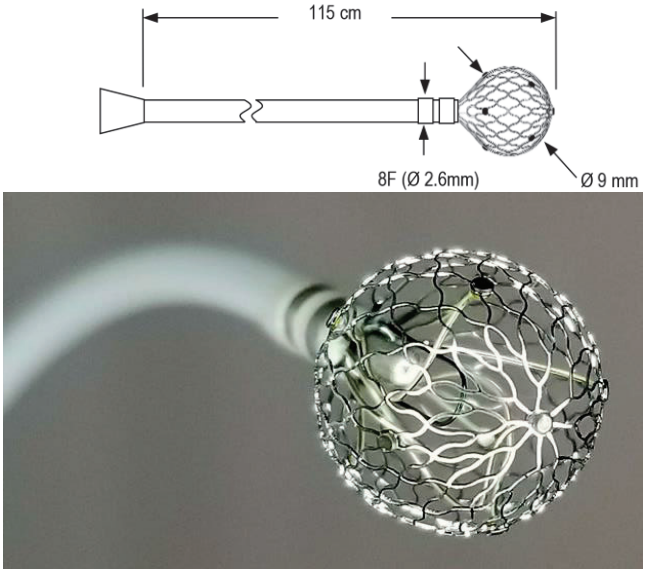

Figure 1 Affera Sphere-9 Ablation Catheter

2.2. AFFERA MAPPING SYSTEM

The Affera Mapping System is a computerized storage and display system with embedded software which is designed to present the user with information regarding the state and location of a cardiac catheter within the body. The system can determine and present the 3-dimensional location of the catheter within the heart using the catheter's electromagnetic location sensor. The location information can be used to create a geometric shell representing chamber anatomy in which a virtual representation of the catheter can be displayed in real time in order to aid navigation of the catheter. The system can also tag location points of interest for reference. Additionally, the system employs an impedance measurement system to measure and display the local impedance of surface electrodes on the Sphere-9 catheter, which can be used as an aid to assess electrode proximity and contact with tissue. The state of impedance of individual electrodes may be presented on a graphical display.

The Mapping System collects and displays electrogram signals from intracardiac electrodes on the catheter and presents voltage data derived from these signals on the display, including overlaying the data on the geometric shell.

2.3. AFFERA RF GENERATOR

The Affera RF Generator is designed to supply RF energy to the Sphere-9 catheter to perform ablation of cardiac tissue. The RF Generator monitors the RF energy delivery during therapy, including the catheter tip temperatures, circuit impedance, output voltage and current, and internal system performance. The application of RF energy can be controlled to a target catheter tip temperature. The RF Generator also monitors the contact quality of the disposable dispersive return electrodes to ensure sufficient electrode contact during therapy delivery. Through a communication link with the Irrigation Pump, the RF Generator can monitor and control the irrigation flow rate prior to, during, and following ablation delivery.

2.4. AFFERA IRRIGATION PUMP AND TUBING SET

The Affera Irrigation Pump and a sterile single-use Tubing Set are used to deliver saline irrigation flow to the ablation catheter during RF energy delivery. The Pump interfaces with the RF Generator via a communication link to enable automatic control of the irrigation flow rate prior to, during, and following ablation delivery. The communication link also allows for Pump status updates including notification of interruption of the irrigation flow due to air bubble detection or other fault conditions.

Additional information involving the device and its components including pre-clinical data can be found in the Investigator's Brochure.

2.5. INDICATIONS FOR USE

The Affera Sphere-9 Ablation Catheter and the Affera Mapping and Ablation System are indicated for cardiac ablation and mapping (stimulation and electrogram recording) in patients with cardiac arrhythmia.

3. GOOD CLINICAL PRACTICES (GCP) STATEMENT

This trial will be conducted in compliance with the Investigational Plan, the signed clinical study agreement and with the ethical principles stated in the latest version of the Declaration of Helsinki (2013), the applicable guidelines for good clinical practices, MEDDEV 2.7/4 (Guidelines on Clinical investigations: a guide for manufacturers and notified bodies) and 2.7/3 (Clinical investigations: serious adverse event reporting), EN ISO 14155:2012 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), or the applicable local and international regulations, whichever provide the greater protection of the individual. Any deviations from the Investigational Plan that

may affect the safety and welfare of study participants will be immediately reported to the Sponsor and to the Ethics Committee (EC) per each institution's guidelines.

4. RISK-BENEFIT ANALYSIS

The anticipated adverse events associated with cardiac ablation procedures include events reported in the literature related to catheter procedures, events identified in the risk and hazard analyses, and events associated with percutaneous interventions, and therefore represent the risks associated with participation in the trial. A list of anticipated adverse events is defined in the Anticipated Adverse Events Section 7.5 of this document.

Potential device malfunctions and potential user errors have been identified in the Hazard Analysis and Failure Modes and Effects Analysis exercises conducted in accordance with ISO 14971. These are technical complications that may occur with the devices. Mitigating steps to address each of the potential device malfunctions and potential user errors have been implemented to reduce the risks as low as possible. No residual risks remain that are higher than the risks associated with the use of currently available conventional cardiac mapping and ablation tools.

Overall potential patient benefits include reduction in symptomatic episodes of arrhythmia, similar to currently available cardiac ablation systems. Potential patient risks include adverse events and potential device malfunctions and potential user errors similar to those associated with commercially available cardiac ablation systems.

It is believed that the potential risks to a patient participating in this study should be similar to other RF ablation systems for the treatment of AF. Eligibility criteria that exclude patients who are at higher risk for experiencing an anticipated adverse event have been selected to reduce the potential risks to patients participating in this study.

5. INVESTIGATIONAL PLAN

5.1. STUDY OBJECTIVES

The objectives of this study are to evaluate the safety and performance of the Sphere-9 Ablation Catheter and the Affera Mapping and Ablation System.

5.2. STUDY DESIGN

This is a prospective, single-arm, single center study involving the Affera Sphere-9 Ablation Catheter and the Affera Mapping and Ablation System in up to 30 patients. The arrhythmias treated in this study are common atrial arrhythmias: atrial flutter (AFL), paroxysmal atrial fibrillation (AF), and persistent atrial fibrillation.

The primary safety outcome is the rate of the following serious adverse events (SAEs) occurring starting Day 0 and extending through the Day 10 assessment:

transient ischemic attack; cerebrovascular accident; major bleeding; cardiac tamponade; pulmonary vein stenosis; severe pericarditis requiring extended hospitalization; myocardial infarction; diaphragmatic paralysis; atrio-esophageal fistula (through the Day 90 assessment); valvular damage; phrenic nerve palsy; intra-procedural device complications requiring open chest or heart surgery; vascular complications requiring surgical intervention; and death.

The primary product performance outcome is determined during the procedure and includes catheter handling, 3D electro-anatomical map creation and utility sufficient to aid diagnosis, and generation of acceptable acute therapeutic RF lesions.

The secondary product performance outcome is freedom from the treated arrhythmia detected by ambulatory monitoring or ICD interrogation at the Day 90, Day 180, and Day 365 Visits. In AF subjects, this includes freedom from documented AF, AT, or AFL.

Pre-screening, i.e., medical record review without obtaining informed consent, is allowed.

Initial Screening Activities. After providing informed consent, initial screening consisting of review of relevant history including duration and frequency of arrhythmia(s), their subsequent treatments (e.g., medications, previous ablation) and associated symptoms will be performed.

If the subject passes the initial screening, remaining screening tests will be performed which include assessment of study eligibility, demographics, concomitant use of antiarrhythmic drugs (AADs) and other important cardiovascular drugs, physical exam, vital signs, 12 lead EKG, hematology, transthoracic echocardiography (TTE), urine pregnancy test (women of childbearing potential only), and optional CT and/or MR imaging

After confirmation of the absence of atrial thrombus precluding catheter introduction, eligible subjects will undergo mapping and ablation. Subjects will be assessed for potential adverse events prior to discharge. Esophageal evaluation, and CT and/or MR imaging may optionally be performed after treatment or during follow-up.

Subjects will be followed for approximately 365 days after the ablation procedure to characterize safety and product performance. Note, the Day 10 visit can be conducted by telephone. Ambulatory monitoring for a minimum of 48 hours will be conducted within the follow-up windows at Day 90, Day 180, and Day 365. Use of antiarrhythmic drugs and other important cardiovascular drugs will be collected at every visit. Serious adverse events (AEs) will be collected starting on Day 0 through study exit.

A summary of the schedules of evaluations and visits can be found in Appendix 1.

5.3. SUBJECT POPULATION

Up to a total of 30 subjects meeting the following study entry criteria will be treated.

5.3.1. INCLUSION CRITERIA

Subjects must satisfy all inclusion criteria to be included in the study:

1. Age ≥ 18 and ≤ 75 years.
2. Suitable candidate for catheter non-emergent mapping and ablation of atrial flutter or atrial fibrillation as follows:

   - Atrial Flutter defined as
     - At least one episode of typical (clockwise or counterclockwise) atrial flutter documented by EKG, 12 lead EKG, Holter or transtelephonic monitor, telemetry strip, or implanted device within 6 months prior to enrollment.

     OR
   - Atrial Fibrillation defined as
     - History of symptomatic paroxysmal and/or persistent atrial fibrillation within the past year documented by EKG

       AND
     - Failure of at least one class I-IV drug as evidenced by recurrent symptomatic AF, or intolerable to AAD.

3. Subject is able and willing to give informed consent.
4. Subject is able and willing, and has ample means to comply with all pre-, post- and follow-up testing requirements.

5.3.2. EXCLUSION CRITERIA

Subjects ***will not be eligible for the study*** if any of the following criteria are present:

1. Documented left atrial thrombus or another abnormality which precludes catheter introduction.
2. Documented ejection fraction (EF) < 40%.
3. Contraindication to anticoagulation therapy (heparin, warfarin, or novel oral anticoagulant [NOAC]).
4. Unstable angina or ongoing myocardial ischemia.
5. Myocardial infarction, unstable angina, cardiac surgery or coronary intervention within 3 months of enrollment.
6. Congenital heart disease where the underlying abnormality increases the risk of the ablation.
7. Pulmonary hypertension (mean pulmonary artery pressure [mPAP] > 50 mmHg)
8. Enrollment in any other ongoing study protocol that would interfere with this study.

9. Documented severely impaired kidney function defined as Cockcroft-Gault Glomerular Filtration Rate (GFR) < 29ml/min.
10. Active gastrointestinal (GI) bleeding
11. Active infection or sepsis.
12. Short life expectancy (< 1 year) due to illness such as cancer, pulmonary, hepatic or renal disease.
13. Significant anemia (defined as hemoglobin < 8.0 gr/dL).
14. Severe uncontrolled systemic hypertension with systolic blood pressure (SBP) > 200 mm Hg within last 30 days.
15. Severe bleeding, clotting or thrombotic disorder.
16. Uncontrolled diabetes.
17. Women who are pregnant or are not willing to use contraception for the duration of the study.
18. Severe chronic obstructive pulmonary disease (COPD; identified by a forced expiratory volume [FEV1] <1).
19. Prior stroke or TIA within the last 6 months.
20. Any other condition that, in the opinion of the investigator, poses a significant hazard to the subject if an ablation procedure was performed.

Additional exclusion criteria for AF patients only:

21. Left atrial diameter of > 55 mm (parasternal view).
22. Prior atrial septal defect (ASD) or patent foramen ovale (PFO) closure with a device using a transcatheter percutaneous approach.
23. Hypertrophic cardiomyopathy defined as left ventricular (LV) septal wall thickness >1.5cm.
24. Prior ablation or surgery for atrial fibrillation.
25. NYHA Class III or IV

5.4. STUDY PROCEDURES

Prior to recruitment of any subjects into the study, written approval of the protocol and informed consent must be obtained from the EC.

5.4.1. INFORMED CONSENT

The investigator will explain the study purpose, procedures, and subject's responsibilities to the potential participant and/or legal representative. Informed consent must be obtained from each subject prior to conducting any study related procedures including screening procedures that are not part of the standard of care at the institution. The subject's willingness and ability to meet the follow-up requirements will be determined, and written informed consent will be obtained. The subject will sign and date the informed consent form. The investigator will also sign and date the consent form. The original informed consent form will be retained with the subject records; a copy will be provided to the subject or legal representative.

Following is a detailed list of study visits from screening to final follow-up and the required procedures/tests. Methodologies for specific tests/procedures are described in Section 6.

5.4.2. SUBJECT IDENTIFICATION

To maintain confidentiality, the subject's name should not be recorded on any study document other than the informed consent form. A subject is considered enrolled after informed consent has been obtained. Each enrolled subject will be assigned a unique identifier in the following format: CP00001-XX-YYY. CP00001 is the study number, XX is the 2-digit assigned site number, and YYY is the 3-digit sequential subject ID number starting with 001. For example, the first subject at site 01 will be assigned CP00001-01-001. Subject ID numbers will not be re-used (e.g., if the subject is determined to be a screen failure).

5.4.3. VISIT 1: SCREENING (DAY -30 TO DAY 0)

Screening should be completed within 30 days of the index ablation procedure. Test results from routinely performed standard assessments may be used to determine eligibility. Prior to screening, the subject will provide informed consent and then be ***initially*** screened by review of relevant medical history including duration and frequency of arrhythmia(s), their subsequent treatments (e.g., medications, previous ablation) and associated symptoms.

If initial screening criteria are met, screening will proceed. Eligibility will be assessed sequentially, starting with the least invasive and least expensive tests as follows. ***Results from each test / screening activity should be reviewed prior to proceeding to the next step.***

- Demographics
- Concomitant use of AADs and other important cardiovascular drugs medications
- Physical exam, including actual height
- Vital signs
- 12 lead EKG
- Labs:
  - Urine pregnancy test (for women of childbearing potential only)
  - Hematology
- Transthoracic echocardiography (TTE)
- Optional CT or MR imaging

5.4.3.1. SCREEN FAILURES

Subjects not meeting all study entry criteria will be designated as screen failures. End of study procedures will not be performed for these subjects, but their reason for ineligibility will be recorded on the Screening Log. Screen failures are not counted towards to total study enrollment.

5.4.4. VISIT 2: DAY 0 – INDEX ABLATION PROCEDURE

After documenting concomitant use of AADs and other important cardiovascular medications and confirming the absence of atrial thrombus or another abnormality precluding catheter introduction, catheters are introduced percutaneously and advanced to the chamber of interest. For left atrial procedures, if the esophagus is not mechanically deviated away from the left atrium, a temperature probe may be placed in the esophagus to monitor heating during the procedure.

The heart chamber is mapped using the Affera Sphere-9 Ablation Catheter and the Affera Mapping System to generate a representation of the heart and to locate the areas of the heart that are creating or propagating problematic electrical signals that interfere with the proper rhythm. In addition, pacing is used to identify the location of the phrenic nerve.

Ablation using the Affera Sphere-9 Ablation Catheter and the Affera RF Generator is performed, and data regarding ablation delivery is recorded by the Affera Mapping System. Procedural success is monitored by mapping and/or pacing to verify termination and non-inducibility of the arrhythmia (all subjects) and/or successful isolation of target pulmonary veins. Any serious procedural adverse events (AEs) will be documented.

Prior to discharge, the following will be documented:

- Vital signs
- 12-lead EKG
- Serious adverse events (AEs)

At the discretion of the investigator, the following assessments can be performed prior to discharge:

- Transthoracic echocardiography (TTE)
- Endoscopic evaluation of the esophagus
- CT or MR imaging

5.4.5. VISIT 3: DAY 10 ± 3 DAYS (TELEPHONE CALL)

The following assessments will be performed, optionally via a telephone call:

- Concomitant use of AADs and other important cardiovascular medications
- Serious cardiovascular AEs

5.4.6. VISIT 4: DAY 90 ± 14 DAYS

The following assessments will be performed:

- A minimum of 48 hours of ambulatory cardiac monitoring
- Episodes of treated arrhythmia greater than 30 second in duration
- Concomitant use of AADs and other important cardiovascular medications
- 12 lead EKG
- Serious cardiovascular AEs

At the discretion of the investigator, CT or MR imaging can be performed at this visit.

5.4.7. VISIT 5: DAY 180 ± 30 DAYS

The following assessments will be performed:

- A minimum of 48 hours of ambulatory cardiac monitoring
- Episodes of treated arrhythmia greater than 30 second in duration
- Concomitant use of AADs and other important cardiovascular medications
- 12 lead EKG
- Serious cardiovascular AEs

At the discretion of the investigator, CT or MR imaging can be performed at this visit.

5.4.8. VISIT 6: DAY 365 ± 30 DAYS

The following assessments will be performed:

- A minimum of 48 hours of ambulatory cardiac monitoring
- Episodes of treated arrhythmia greater than 30 second in duration
- Concomitant use of AADs and other important cardiovascular medications
- 12 lead EKG
- Serious cardiovascular AEs

At the discretion of the investigator, CT or MR imaging can be performed at this visit.

All subjects will exit the study after the Day 365 visit.

5.5. STUDY COMPLETION

5.5.1. COMPLETED SUBJECTS

Each subject in the study will be considered completed when all assessments through the Day 365 visit have been performed in accordance with the study protocol.

5.5.2. DISCONTINUED SUBJECTS

Any subject may voluntarily discontinue the study at any time without prejudice. The investigator may discontinue a subject from the study at any time if (s)he considers that remaining in the study compromises the subject's health or the subject is not sufficiently cooperative. In either event, reason(s) for discontinuation should be recorded.

Possible reasons for study discontinuation include the following:

- Adverse events (AEs) necessitating discontinuation from the study.
- Repeat ablation with a non-study device.
- Subject decision (specify).
- Investigator decision (specify).
- Other reason (specify).

The reasons for any subject discontinuation will be recorded on the study completion form of the study worksheets. If possible, subjects who withdraw prior to study completion will undergo the following:

- 12 lead EKG
- AE assessment
- Assessment of symptomatic episodes of the treated arrhythmia
- Concomitant medications

Lost to follow-up will only be considered at the Day 365 visit. Other follow-up visits will be considered missed visits if the subject is unable to attend. Every attempt must be made to have subjects complete the study. The investigator/designee must do his/her best to contact the subject by phone at least twice. If no response is obtained from the subject, the investigator/designee is encouraged to contact one of the subject's relatives or his/her general practitioner. Documentation of these contacts must be recorded in the subject's source.

5.5.3. PREMATURE STUDY TERMINATION

The Sponsor reserves the right to discontinue the study for any safety, ethical or administrative reason at any time.

5.6. INVESTIGATIONAL DEVICE ACCOUNTABILITY

Documentation of receipt, use and return of all Sphere-9 Ablation Catheters as well as the Affera Mapping and Ablation System must be maintained by the Principal Investigator (PI) or his/her designee. Investigational devices are to be used only in accordance with this protocol and under supervision of the PI or a duly designated person. It is the PI's responsibility to ensure that all study devices are kept in a secure location, with access limited to individuals authorized by the investigator. A record of all study devices received, used and returned must be maintained by the site until the conclusion of the study. Following accountability of the study devices by the Sponsor or its designee, all unused study devices will be returned to the Sponsor/Designee as directed in writing by the Sponsor or designee for gross reconciliation.

5.7. PRIOR AND CONCOMITANT MEDICATION

All concomitant antiarrhythmic drugs (AAD) and other important cardiovascular medications (taken within 30 days of Day 0) will be recorded at each visit. For each medication taken, the following information will be collected:

- Medication trade or generic name;
- Indication for which the medication was given;
- Dose/strength, route, and frequency of administration;
- Date started, and date stopped (or continuation at study exit).

6. EXAMINATIONS AND EVALUATIONS

6.1. EVALUATIONS CONDUCTED AT SCREENING ONLY

6.1.1. DEMOGRAPHICS

Date of birth, gender, race and ethnicity will be recorded.

6.1.2. MEDICAL HISTORY

Relevant medical history including duration and frequency of arrhythmia(s), their subsequent treatments (e.g., medications, previous ablation) and associated symptoms will be obtained at Screening. All positive and negative findings will be carefully documented. Any new finding discovered during the Screening evaluation and prior to the index ablation procedure will be considered to be part of the medical history and will not be recorded as an AE.

6.1.3. PHYSICAL EXAM

A physical exam will be performed at Screening. The exam will include the following: head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and gastrointestinal systems. Any abnormalities should be categorized as clinically significant (CS) or not clinically significant (NCS), and the abnormalities should be recorded. Actual height will be measured.

6.1.4. HEMATOLOGY

Laboratory testing will be conducted by a local laboratory at each site at Screening. Hematology evaluation will include: complete blood count (CBC): red blood cells (RBC); hemoglobin (Hgb), hematocrit (HCT), platelets and white blood cells (WBC). Abnormal readings will be considered to be part of the medical history and will not be recorded as an AE.

6.1.5. PREGNANCY TEST (WOMEN OF CHILDBEARING POTENTIAL ONLY)

For women of childbearing potential, a urine beta human chorionic gonadotropin (β-HCG) test will be performed at Screening. Results of the test must be negative. Confirmed menopause is defined as postmenopausal for ≥ 1 year.

6.1.6. OPTIONAL CT OR MR IMAGING

At the discretion of the investigator or the principal investigator, computed tomography (CT) or magnetic resonance (MR) imaging may be conducted during screening. Imaging may also be conducted at any time during the follow-up period. Any clinically significant abnormalities will be recorded.

6.2. EVALUATIONS CONDUCTED DURING THE STUDY

6.2.1. 12 LEAD EKG

A 12-lead electrocardiogram (EKG) will be conducted. The EKG recording will be printed out, and a copy will be placed with subject records. Any clinically significant abnormalities will be recorded.

6.2.2. TRANSTHORACIC ECHOCARDIOGRAPHY (TTE)

A TTE will be conducted at Screening, and may be conducted at the physician's discretion prior to Discharge following the ablation procedure if indicated. At screening, measurements will include EF, LV septal wall thickness (AF patients only), estimation of mPAP, and assessment of left atrial thrombus to the extent possible (AF patients only). Prior to Discharge following the ablation procedure, TTE may be used to assess pericardial effusion. Any (structural) abnormalities should be categorized as clinically significant (CS) or not clinically significant (NCS), and the abnormalities should be recorded.

6.2.3. CONCOMITANT MEDICATIONS

Concomitant AADs and other important cardiovascular medications will be recorded at each visit using the trade name or generic name as described in Section 5.7.

6.2.4. VITAL SIGNS

Vital signs consisting of blood pressure (while subject is sitting), temperature, weight, heart rate, and respiratory rate will be measured.

6.2.5. ATRIAL THROMBUS SCREENING

Prior to the ablation procedure, transesophageal echocardiography (TEE) will be the preferred method to assess left atrial thrombus (for left atrial procedures) and spontaneous echo contrast. Alternatively, if the subject has been on continuous anticoagulation for at least 3 weeks prior to the procedure, intracardiac echocardiography (ICE) may be used to assess cardiac thrombus and spontaneous echo contrast. Any abnormalities should be categorized as clinically significant (CS) or not clinically significant (NCS), and the abnormalities should be recorded.

6.2.6. OPTIONAL ENDOSCOPIC EVALUATION OF THE ESOPHAGUS

At the discretion of the investigator, endoscopic evaluation of the esophagus (gastroscopy) may be conducted to evaluate the extent of esophageal ulceration. Any abnormalities should be categorized as clinically significant (CS) or not clinically significant (NCS), and the abnormalities should be recorded.

6.2.7. AMBULATORY CARDIAC MONITORING

Within the Day 90, Day 180, and Day 365 follow-up windows, each subject will be monitored for a minimum of 48 hours with an ambulatory cardiac monitor. Episodes of atrial fibrillation, atrial flutter, or atrial tachycardia lasting longer than 30 seconds will be noted.

7. EVALUATION OF ADVERSE EVENTS AND DEVICE DEFICIENCIES

7.1. ADVERSE EVENTS DEFINITIONS

An **adverse event (AE)** is the development of an untoward medical occurrence or the deterioration of a pre-existing medical condition following or during exposure to an investigational medical device, whether or not considered causally related to the investigational medical device.

An untoward medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or clinically significant abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).

Conditions or diseases that are chronic but stable should not be recorded as an AE. Changes in a chronic condition or disease that are consistent with natural disease progression are NOT considered AEs and should not be recorded. These medical conditions should be adequately documented in the subject's medical history. However, medical conditions present at enrollment that worsen in intensity or frequency in a manner inconsistent with the natural course of the disease during the treatment or post-treatment periods should be reported and recorded as AEs.

A recurrence of the treated arrhythmia requiring hospitalization in order to administer cardioversion prior to the Day 90 visit is within the scope of treatment for chronic but stable AF patients. This will not be considered an adverse event.

A **serious adverse event (SAE)** is any untoward medical occurrence which:

- Results in death permanent impairment of a body function or permanent damage to a body structure;
- Results in serious deterioration in the subject's health that either:
  - Is life-threatening;
  - Requires inpatient hospitalization (admission to hospital with a stay > 24 hours) or prolongation of hospitalization which is not specifically required by the protocol or is elective;
  - Results in permanent impairment of a body function or permanent damage to a body structure; or
  - Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Additionally, important medical events that may not result in death, be life-threatening or require hospitalization may be considered SAEs when they jeopardize the subject or require medical or surgical intervention to prevent one of the serious outcomes listed above.

Adverse device effect (ADE) is an AE related to the use of an investigational medical device. Note, this definition includes AEs resulting from insufficient or inadequate instructions for use, operation, or any malfunction of the investigational medical device.

In addition, this definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious adverse device effect (SADE) is an ADE that that has resulted in any of the consequences characteristic of a SAE.

An **unanticipated adverse device effect** (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in predicate devices, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.2. ASSESSMENT OF ADVERSE EVENTS

The need to capture AEs is not dependent upon whether or not the clinical event is associated with the use of the study device or procedure. All AEs, regardless of severity, occurring at the index ablation through study exit visit must be recorded. Events occurring prior to the endovascular procedure must be listed in the medical history.

The following information should be obtained for each AE:

1. Event description. Every effort must be made to report the underlying condition or unifying diagnosis for the event. To avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words when possible. Signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs on the CRF (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

In addition, AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause (i.e., a "primary" AE, if clearly identifiable, generally represents the most accurate clinical term to record on AE CRF; events occurring secondary to the primary event should be described in the narrative description of the case [e.g., example: orthostatic hypotension → fainting and fall to floor → head trauma →neck pain; the primary AE is orthostatic hypotension]).

2. Duration: The date of onset and date of resolution should be reported. Every effort should be made to capture the exact dates.

3. Outcome: The final status of the event should be reported as resolved, ongoing, or if it resulted in death. If the event is present at the final study visit, the ongoing box must be marked.

4. Severity: The worst severity of the event must be reported as mild, moderate, or severe using the following definitions:

- **Mild:** Aware of sign or symptom, but easily tolerated
- **Moderate:** Discomfort enough to cause interference with usual activity
- **Severe:** Incapacitating with inability to work or do usual activity

5. Action taken: Treatment of the event may be reported as none, medical and/or surgical.

6. Seriousness: Determined by using the criteria in Section 7.1.

7. Relationship to device (study device or ancillary device), and procedure. The relationship to device and study procedure will be assessed using the following criteria.

- **Not related:** no temporal association, or the cause of the event has been identified; or the device or procedure cannot be implicated
- **Unlikely**: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained
- **Possible:** temporal association, but other etiologies are likely to be the cause; however, involvement of the device or procedure cannot be excluded
- **Probable**: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained
- **Causal:** temporal association; other etiologies are possible, but unlikely

If any AE is considered to be "possibly related" or "related" to the use of the study device, that event will classed as an ADE or a SADE.

7.3. REPORTING/RECORDING OF AES

Throughout the course of the study, all efforts will be made by the investigator to remain alert to possible AEs. The first concern will be the safety of the subject, and for providing appropriate medical intervention. The period of observation for collection of AEs starts at index ablation procedure until study exit. Any AE should be recorded on the appropriate study worksheet.

7.4. ADVERSE EVENTS REQUIRING EXPEDITED REPORTING

The Investigator will report all SAEs and device deficiencies that could have led to a SADE; this information shall be promptly followed by detailed written reports [EN ISO 14155:2012 § 9.8 b].

The Investigator will document all SAEs and SADEs, including device deficiencies in the study subject's file and report it to the Sponsor and to the Clinical Research Organization (CRO) within 24 hours of knowledge of event. When medical reports (lab results, examinations, etc.) associated with AEs are submitted to the Sponsor or

CRO, all personal subject information (name, address, etc.) ***must*** be removed or redacted. The redacted materials must be identified only with the subject ID number.

Upon notification of SAEs, the Sponsor will initiate and complete a review and evaluation of the event within time frames that will maintain reporting compliance with applicable regulatory agencies. The Sponsor is responsible for classification and reporting of AEs and ongoing safety evaluation of the clinical investigation in line with EN ISO 14155:2012 and regulatory requirements. If insufficient information is available to reach a definitive diagnosis, the Sponsor may instruct the monitor responsible for the site to contact the site to request additional confirmatory information, if any.

In the event of a subject's death, the Investigator will make reasonable effort to obtain a copy of the autopsy report and/or death summary. The Investigator will determine the cause of death and its relationship to the investigational device; the Investigator will record results on the AE case report form (CRF). The Investigator will include copies of an autopsy report, if available, and/or a death summary with this form.

The Investigator is responsible for reporting all SAEs, SADEs, and device deficiencies that could have led to a SADE to the EC, according to national regulations and EC requirements. The investigator will forward a copy of this report to the Sponsor and file it in the site regulatory binder.

The Sponsor will ensure that its Authorized Representative will report all SAEs and device deficiencies that could have led to an SADE to the Competent Authorities in accordance with European Medical Devices directives and all applicable national regulations.

7.5. ANTICIPATED ADVERSE EVENTS

Anticipated complications/AEs are defined as complications/events that can be reasonably associated with catheter ablation procedures.

Anticipated AEs include, but are not limited to:

- Air embolism
- Allergic reaction (including anaphylaxis)
- Anesthesia reaction
- Angina
- Aorto-right atrial fistula
- Arrhythmias, including exacerbation of pre-existing atrial fibrillation
- Arterial-venous fistula
- Cardiac perforation/ tamponade
- Cardiac thromboembolism
- Cardiac or respiratory arrest
- Catheter entrapment

- Cerebrovascular incident / Stroke
- Chest pain/discomfort
- Congestive heart failure
- Coronary artery dissection
- Coronary artery spasm
- Coronary artery thrombosis / occlusion
- Death
- Diaphragmatic paralysis
- Dislodgement of ICD or permanent pacing leads
- Endocarditis
- Esophageal ulceration
- Gastroparesis
- Heart failure / pump failure
- Hemoptysis
- Hemoptysis
- Hemothorax
- Hypotension
- Hospitalization (initial and prolonged)
- Increased creatinine phosphokinase (CPK) level
- Infections
- Laceration
- Leakage of air or blood into the lungs or other organs due to perforation
- Left atrial esophageal fistula
- Major bleeding, requiring surgery or transfusion
- Myocardial infarction
- Obstruction or perforation or damage to the vascular system
- Pericarditis
- Pericardial effusion
- Phrenic nerve damage including Diaphragmatic paralysis
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pulmonary edema
- Pulmonary embolism
- Pulmonary vein dissection
- Pulmonary vein thrombus
- Pulmonary hypertension
- Respiratory depression
- Skin burns
- Severe PV stenosis or complete occlusion, even asymptomatic
- Tamponade, potentially requiring surgery
- Temperature elevation or fever
- Transient Ischemic Attack (TIA)
- Thromboembolism

- Thrombosis
- Unintended complete or incomplete AV, Sinus node, or other heart block or damage
- Valve damage
- Vascular bleeding / local hematomas / ecchymosis
- Vasovagal reactions
- Ventricular tachyarrhythmia
- Volume overload

7.6. DEVICE DEFICIENCIES

Device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note, device deficiencies include malfunctions, use errors, and inadequate labelling. All device deficiencies or malfunctions that occur during the course of the trial and could have led to an SAE must be reported, whether or not they were associated with an AE.

Device malfunction: failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use.

User error: act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

The Device Deficiency CRF is specific for reporting all device deficiencies, or malfunctions that occur during the course of the trial, whether or not they were associated with an adverse event. Device Deficiency CRFs should be submitted to the Sponsor and CRO within 24 hours of the occurrence defining the device deficiency.

Anticipated device deficiencies and malfunctions include but are not limited to:

- Catheter deflection deficiency or failure
- Malfunction of a catheter electrode
- Malfunction of a catheter temperature sensor
- Unexpected termination of ablation due to internal system error
- Failure to initiate ablation due to internal system error
- Temporary or sustained loss of catheter navigation/visualization capability

8. STATISTICAL METHODS

8.1. SAMPLE SIZE CALCULATION

This trial is intended to demonstrate safety and performance of the device and system. As a result, no formal statistical hypothesis was applied to derive to the sample size.

8.2. STUDY OUTCOMES

8.2.1. SAFETY

The primary safety outcome is the rate of the following SAEs occurring starting Day 0 and extending through the Day 10 follow-up visit:

- TIA
- CVA
- Major bleeding
- Cardiac tamponade
- Pulmonary vein stenosis
- Severe pericarditis requiring hospitalization
- Myocardial infarction
- Diaphragmatic paralysis
- Atrio-esophageal fistula (through the Day 90 assessment)
- Valvular damage
- Phrenic nerve palsy
- Intra-procedural device complications requiring open chest or heart surgery
- Vascular complications requiring surgical intervention
- Death

8.2.2. DEVICE PERFORMANCE

The primary product performance outcome is determined during the procedure, and is defined as the following:

- Catheter handling sufficient to reach reasonable intended targets, as determined by the physician:
  - catheter delivery to the desired cardiac chambers
  - manipulation of catheter
  - completion of mapping procedure
  - safe removal of catheter from the subject
- 3D electro-anatomical map creation and utility sufficient to aid diagnosis
- Generation of acceptable acute therapeutic RF lesions

The secondary product performance outcome is freedom from documented recurrence of the treated arrhythmia detected by ambulatory monitoring at the Day 90, Day 180, and Day 365 Visits. In AF subjects, this includes freedom from documented recurrence of AF, AT, or AFL. Recurrence is defined as any episode lasting longer than 30 seconds.

8.3. DESCRIPTIVE ANALYSES

Continuous variables will be summarized using standard quantitative statistics: number of non-missing observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations, if any, will also be summarized.

Categorical variables will be summarized using classical frequency statistics: number of non-missing observations and percentages by categories. Number and percent of missing data, if any, will also be summarized.

9. STUDY CONDUCT

9.1. ETHICS COMMITTEE (EC)

Prior to the initiation of the study, the protocol, and the informed consent form will be submitted to the EC for approval. By signing the clinical trial agreement, the investigator is assuring that an EC will be responsible for the initial and continuing review of the proposed clinical study. A copy of the EC approval letter for the protocol, the informed consent, and the protocol signature page must be submitted to the Sponsor or its designee prior to release of investigational supplies to the study site. The approval letter must refer to the specific protocol and the informed consent form. Any Investigator who is also a member of the EC is not to participate in the protocol approval decision. This non-participation must be noted in the approval letter. The study site must maintain an accurate and complete record of all reports, documents and other submissions made to the EC concerning this protocol.

Any report of withdrawal of EC approval will be submitted to the Sponsor or its designee within five (5) working days.

9.2. COMPETENT AUTHORITY

If needed, the study will be reviewed by the relevant Competent Authority as well. The Sponsor or its designee is responsible for obtaining regulatory approval for the study from the relevant Competent Authority. No subjects may be enrolled in the study until written notification of such approval has been given by the Sponsor. The Sponsor or its designee is responsible for reporting SAE and Device Deficiencies that might have led to a SADE as appropriate to the relevant Competent Authority. The Sponsor or its designee is responsible to provide the relevant Competent Authority with the study final report within 90 days of the study termination.

The study will not start without the written approval of the EC and, where needed, the Competent Authority approval and after the completion of any other local regulation requirements.

9.3. INFORMED CONSENT PROCESS

It is the responsibility of the Investigator to inform each subject or his/her legal representative, prior to the screening evaluation, of the purpose of this clinical trial, including possible risks and benefits and document the informed consent process in the subject's chart. Any changes made to the informed consent must be approved by the Sponsor or its designee, prior to submission to an EC. After approval by the Sponsor or its designee, the informed consent must be submitted to and approved by an EC. Prior to entry into the study or initiation of any study-related procedures, the subject or his/her legal representative must read, sign and date the informed consent form. The person executing the consent must also sign and date the EC-approved consent form. One original informed consent form is to be retained by the study site and a copy is to be given to the subject or his/her legal representative. The informed consent process must be documented in the subject's source/medical record.

The informed consent must be written in a language in which the subject or his/her legal representative is fluent. If a foreign language translation is required, a statement of certification of the translation must be issued. Regulations require that foreign language informed consent forms be submitted to the EC for approval. The investigator must forward a copy of the consent form, the certified foreign language translation and an EC approval letter to the Sponsor or its designee.

9.4. CONFIDENTIALITY

In accordance with GCP and with the national data protection laws, all information concerning the subjects in the study must be treated as strictly confidential by all persons involved in the study. Health data will be recorded and forwarded to the Sponsor or its designee, participating EC and Competent Authorities, for evaluation as required. Any information that is obtained in connection with this study that can be identified with the subjects will remain confidential. Any data that may be published in scientific journals will not reveal the identity of the study participants

The investigator acknowledges that any and all information acquired from the Sponsor or its designee or developed or acquired in connection with the study are strictly confidential. The investigator will not disclose any confidential information to any third party nor use confidential information for any purpose without first obtaining the consent of Sponsor in writing. Such consent shall be deemed to have been given for disclosure to any person for whom the investigator is responsible at his/her center, but only so far as required for the purposes of the study, and, in the case of disclosures to staff, only if such staff are bound by obligations of confidentiality no less strict than those set out herein.

9.5. INSURANCE

In order to cover possible damage to health, in relation to participation in this study, the Sponsor, has, as required by law, obtained appropriate insurance coverage.

9.6. PROTOCOL DEVIATIONS

The Investigator is not allowed to deviate from the protocol without prior approval by the Sponsor and prior review and documented approval from the governing EC.

Under emergency circumstances, deviations from the clinical investigation plan to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the EC. These deviations will be reported to the Sponsor and to the EC as soon as possible after detection, but no later than 24-hours from the time of the deviation.

Deviations must be documented on the appropriate Protocol Deviation CRF. If a Clinical Monitor becomes aware that an Investigator is not complying with the signed Investigator's Agreement, the Investigational Plan, the requirements of ISO 14155 or other applicable regulations, or any conditions of approval imposed by the reviewing EC, the Sponsor or designee will immediately either secure compliance or discontinue shipments of the investigational device to the Investigator and terminate the Investigator's participation in the investigation. The Investigator will be required to return all investigational components of the study device and system, unless this action would jeopardize the rights, safety or welfare of a patient.

Protocol deviations will be analyzed by the Sponsor for the impact to the overall integrity of the study. Disqualification is warranted when an Investigator has repeatedly or deliberately violated governing regulations or has repeatedly or deliberately submitted false information in any report. Where protocol deviations occur, which do not warrant disqualification from a study, the Sponsor or designee will implement appropriate corrective and preventive actions, including repeat training as deemed necessary.

9.7. STUDY MONITORING AND SOURCE DOCUMENTATION

The Sponsor or its designee may meet with investigators prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator with the study protocol.

During the study, the clinical monitor will visit the study facilities regularly and utilize telephone and written communications on an ongoing basis to maintain current knowledge of the study. During periodic visits to the study site, the monitor will review the source documents used for completion of the CRFs to verify the accuracy and completeness of the information contained in those reports in preparation for retrieval. Source documents must contain all data entered in the CRFs. Source documents may include a subject's medical record, hospital charts, clinic charts, the Investigator's study files, the results of diagnostic tests such as laboratory tests, EKGs, 24-hour Holter monitoring and the like. All data generated during this study and the source documents from which they originated are subject to inspection by the Sponsor or its representatives and/or regulatory agencies.

Upon completion of the study, the clinical monitor will conduct a final visit (close-out) to the site. The objectives of this visit are to ascertain that all regulatory records and reports are complete, verify that investigational devices and other supplies have been accounted for and ensure that the investigator is aware of his/her responsibilities post-study.

9.8. PROTOCOL AMENDMENTS

The Sponsor will document modifications to the protocol in the form of a written amendment. Protocol modifications that impact subject safety or the validity of the study must be approved by the EC before implementation. In the case of a medical emergency, to remove immediate apparent hazard to subjects, a change may be made preferably after discussion with the Sponsor or its designee. In these instances, the EC and, if applicable, Competent Authorities will be notified as soon as possible.

9.9. RECORD KEEPING AND RETENTION

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the study site, the Sponsor and its representatives and relevant health authorities/regulatory agencies. All reports and communications relating to study subjects will identify subjects only by initials and subject identification number. Complete subject identification will be kept by the investigator. This information will be treated with strict adherence to professional standards of confidentiality.

All study-related records must be maintained for at least 5 years after study completion. The Sponsor will notify the Investigator when records are no longer needed. The Investigator will not discard any records without notifying the Sponsor. If the Investigator moves from the current investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

9.10. INVESTIGATOR FINAL REPORT

The investigator shall provide the EC and the Sponsor with an accurate final report within 2 months after completion, termination or discontinuation of the study. The final report may not precede final data submission which has not been monitored.

9.11. STUDY REPORT AND PUBLICATION

The results of the study may be submitted for publication. Upon the prior written consent of Sponsor, Investigator shall have the rights to publish papers related to the Study.

If written permission from the Sponsor is provided, the PI may publish and/or present the results of the Study conducted at their site, provided that, prior to any such publication or presentation, the site and/or the PI shall furnish the Sponsor with two (2) hard copies and one electronic copy of any materials intended for publication

or presentation at least sixty (60) days prior to the submission of manuscripts. The Sponsor shall then have sixty (60) days from the receipt of such materials to review and provide the site and/or the PI with written comments.

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Rev	CO	Description of change
A	CO-000964	Release of Protocol CP-00001A revision 2: define as single center study; add ambulatory monitoring at 3,6 and 12 months; add pacing to identify phrenic nerve; add gastroscopy; remove TTE from thrombus screening; update safety outcome to 10 days, exclude AF recurrence from AEs.

APPENDICES

Appendix 1. Schedule of Evaluations and Visits

SCHEDULE OF EVALUATIONS AND VISITS

Visit	Screening	Day 0 Ablation Procedure	Day 0 Discharge	Day 10 ± 3 days†	Day 90 ± 14 days	Day 180 ± 30 days	Day 365 ± 30 days
Visit Number	**1**	**2**	**2**	**3**	**4**	**5**	**6**
Informed Consent	✓						
Demographics	✓						
Medical History	✓						
Concomitant Antiarrhythmic Drugs (AAD) and Other Important Cardiovascular Medications	✓	✓		✓	✓	✓	✓
Inclusion/Exclusion	✓						
Physical Exam	✓						
Vital Signs	✓		✓				
12 lead EKG	✓		✓		✓	✓	✓
Hematology	✓						
Urine Pregnancy Test*	✓						
Transthoracic Echocardiography Exam	✓		✓#				
Optional CT or MR imaging	✓#		✓#		✓#	✓#	✓#
Atrial thrombus screening		✓					
Ablation		✓					
Endoscopic Evaluation of Esophagus			✓#				
Serious Adverse Events		✓	✓	✓	✓	✓	✓
Ambulatory Monitoring (48 hours minimum)					✓	✓	✓

* Women of child-bearing potential only
† Telephone call optional
# Optional procedure

Appendix 2. Investigator's Responsibilities

The investigators have the following responsibilities:

1. Subject Selection

The investigator is responsible for assuring that all subjects entering the study conform to the subject selection criteria.

2. Informed Consent

The investigator is responsible for fully reviewing the nature of the study, the possible risks, and alternative treatments with the prospective subject prior to their enrollment in the study. The investigator is responsible for obtaining written Informed Consent for each subject or his/her legal representative, prior to enrollment in the trial. A copy of the signed Informed Consent Form will be maintained in the subject's medical record.

3. Ethics Committee (EC) Approval

The investigator must obtain approval for his participation in this protocol from the EC for the institution at which the procedure will be performed, prior to entering any subjects in the study. The Informed Consent document to be used will also be submitted by the Investigator to the EC for approval prior to initiation of the study. Assurance that the EC approval of the study protocol and Informed Consent has been obtained will be provided to the Sponsor/Designee prior to initiation of the study.

4. Subject Evaluations and Data Reporting

The investigator, or trained designee, is responsible for performing the subject assessments as described in the study protocol. Information generated by these evaluations will be recorded on the CRFs provided by the Sponsor/Designee or entered into the electronic data capture system (EDC) with access provided by the Sponsor/Designee.

Following each subject visit, the CRFs will be completed in a timely manner, e.g., within 48 hours. Original reports from the subject assessments (source documents) will be retained as part of the subject's study file.

Investigator(s) will not deviate from the study protocol without prior approval of the Sponsor/Designee unless protection of the health, safety or welfare of study subjects requires prompt action.

5. Record Retention

In accordance with Commission Directive 2005/28/EC, the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion.

The investigator shall retain the documents for a longer period, where so required by other applicable requirements or by an agreement between the Sponsor and the investigator.

Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the competent authorities.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

6. Investigational Material Accountability

The investigator must maintain accurate records of the receipt of investigational material shipped by the Sponsor/Designee, including the date and lot numbers received. In addition, accurate records must be kept on the amount and date that investigational material, by lot number, was used or returned for each subject in the trial. The investigator must assure that study supplies be used only in subjects enrolled in the study and under the direct supervision of the investigator or co-investigators.

Records of all investigational supplies received, used and returned must be kept by the principal investigator or his/her designee. All unused investigational supplies will be returned to the Sponsor/Designee as soon as practical upon completion of enrollment. Investigational material accounting procedures must be completed before the study is considered terminated.

Appendix 3. Sponsor's Commitments

Affera, Inc. is committed to:

1. Complying with the Declaration of Helsinki, and all applicable health authority regulations governing the conduct of clinical research studies.

2. Protecting the rights, health, safety, and welfare of study subjects.

3. Informing the clinical investigators of any new information about the study, which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.

4. Providing the clinical investigators with the study protocol, and a full set of / access to CRFs on which to document the study evaluation variables for each subject entered into the study.

5. Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.

6. Ensuring equity of consideration among all investigators in multicenter studies in all matters of publications, meeting presentations, etc.

7. Certifying that EC approval of the protocol and completion of the Investigator's Agreement will occur prior to treatment at any investigational site.