# CLINICAL INVESTIGATIONAL PROTOCOL

**TITLE:**

**Single-Laser PVI: Single-encirclement Laserballoon ablation for Pulmonary Veins Isolation**

**STUDY N°:**

**STUDY NAME: Single-Laser PVI**

**VERSION:** 2.0, 27/08/2019

I, the Investigator, have examined this Clinical Investigational Protocol for the Clinical Trial entitled: *Single-Laser PVI: Single-encirclement Laserballoon ablation for Pulmonary Veins Isolation*
I agree to conduct the Clinical Trial according to this Clinical Trial Protocol and to comply with its requirements, subject to ethical and safety considerations.

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DATE: 28-02-2019

SIGNATURE:

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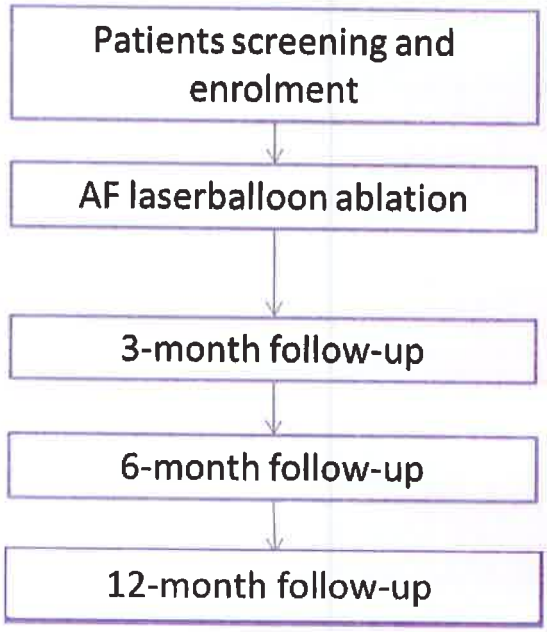
# PROTOCOL SYNOPSIS

| | |
|---|---|
| Title: | Single-Laser PVI: Single-encirclement Laser balloon ablation for Pulmonary Veins Isolation |
| Acronym: | Single-Laser PVI |
| Aim: | To assess the efficacy of laser balloon ablation of atrial fibrillation (AF) without verification of electrical isolation of pulmonary veins using implantable loop recorder. |
| Objectives: | Primary:<br>• Acute and 1-year outcome of the ablation procedure.<br>Secondary:<br>• Assessment of safety and procedural times of the ablation procedure. |
| Endpoints: | Primary:<br>Success rate at 1-year, defined as:<br>• Free from AF, atrial tachycardia and flutter documented with ILR/Holter monitoring without antiarrhythmic drugs.<br>Secondary:<br>- Procedural and 1-year complications related to the ablation procedure.<br>- Absence of AF inducibility with programmed extrastimulation at the end of the procedure, before and after isoproterenol administration.<br>- Procedural time of the ablation procedure.<br>- Fluoroscopy time of the ablation procedure.<br>- Time to first symptomatic AF recurrence.<br>- Time to first asymptomatic AF recurrence.<br>- Need for a redo ablation procedure.<br>- Need for antiarrhythmic drugs.<br>- *AF Burden* quantified with ILR/Holter monitoring at follow-up visits. |
| Study design and duration: | Prospective, open, single-center study<br><br>The patients indicated to AF ablation procedure will be treated with laser balloon ablation and, as per normal clinical practice; the procedure efficacy will be monitored with an ILR,which will be implanted one month (± 15 days) after the ablation procedure, or with evaluation of a cardiac holter monitoring at 3, 6 and 12 months after ablation.<br>The enrolled patients will be followed with 3-month, 6-month and 1-year visits.<br><br>The overall duration of the study is expected to be 24 months with ~ 12 months of enrolment phase. |
| Used device: | - HeartLight Endoscopic Ablation System (CardioFocus, Inc, Marlborough, MA) |

| | |
|---|---|
| Study population | Patients with paroxysmal or persistent AF who have indications for the first time ablation procedure according to the ESC / EHRA recommendations (European Society of Cardiology / European Heart Rhythm Association). |
| Inclusion/Exclusion criteria | Inclusion criteria<br>1. Age between 18 and 85 years<br>2. Paroxysmal or persistent AF<br>3. Patients AF who have indications for the first time ablation procedure according to the ESC / EHRA recommendations (European Society of Cardiology / European Heart Rhythm Association).<br>4. Ability to provide written informed consent for study participation and be willing and able to comply with the study evaluations and follow up schedule<br><br>Exclusion criteria<br>1. Previous AF ablation procedures<br>2. Secondary AF due to other causes<br>3. Hyperthyroidism<br>4. Left ventricular ejection fraction <30%<br>5. NYHA class IV<br>6. Left atrium area > 35 $cm^2$<br>7. Severe disease of cardiac valves<br>8. Contraindication to anticoagulant therapy<br>9. Presence of thrombus in the left atrium<br>10. Myocardial infarction or unstable angina or recent coronary artery bypass (<6 months)<br>11. Thoracic surgery for congenital, valvular or aortic disease<br>12. History of cerebrovascular events<br>13. Pregnancy<br>14. Significant comorbidity, such as cancer, severe kidney failure requiring dialysis, severe obstructive pulmonary disease, cirrhosis, with a life expectancy of less than 2 years<br>15. Contraindications are present as indicated in the "instructions for use" of the devices used |
| Statistical considerations | In a recent meta-analysis including 1188 patients, free from arrhythmic recurrences at 12 months after a single ablative procedure with a laser balloon and without continuous monitoring with ILR was 74%[1].<br><br>Assuming that the approach without post-ablative verification of pulmonary vein isolation and continuous monitoring with ILR/Holter ECG can lead to a 60% success rate at 12 months, 80 patients are required to have an 80% probability to observe a level of 2-code significance of 0.05 in an exponential model with the log rank test. With an estimated loss of data (patients lost to follow-up, protocol deviations and incomplete data) of 5%, the total number of patients to be enrolled is 82.<br>Descriptive statistics (arithmetic mean, median as indicated, minimum and maximum and standard deviation) will be calculated for quantitative variables. Absolute frequencies and percentages will be obtained for qualitative variables. Summary statistics and 95% confidence intervals |

| | |
|---|---|
| | will be presented. Unpaired the Student's t test will be used to compare continuous variables and with the chi-square test for categorical variables, as appropriate. All tests are two-tailed.<br>A detailed statistical analysis plan will be finalized before performing the analysis. |
| Data collection | - Before ablation procedure: collection of standard data for patients undergoing AF ablation.<br>- During ablation procedure: procedural and fluoroscopy times.<br>- After ablation procedure: arrhythmic recurrences at 3-month, 6-month and 1-year follow-up. |

## 1. STUDY FLOW CHART



| | Screening Enrolment | Procedure | Discharge | 3M FUP | 6M FUP | 1Y-FUP |
|---|---|---|---|---|---|---|
| Inclusion/Exclusion criteria | X | | | | | |
| Informed consent | X | | | | | |
| Medical history, demographic data, drug therapy | X° | | | | | |
| 12-lead ECG | X° | X° | X° | X° | X° | X° |
| Echocardiography | X° | | | X° | X° | X° |
| Holter ECG | | | | X° | X° | X° |
| Pregnancy test | X° | | | | | |
| AF burden | | | | X° | X° | X° |
| Symptoms | X° | X° | X° | X° | X° | X° |
| Ablation procedure times | | X | | | | |
| AF/AT recurrences | | | | X° | X° | X° |
| Adverse events | | X° | X° | X° | X° | X° |
| Antiarrhythmic drugs | X° | X° | X° | X° | X° | X° |

M= Month
Y= Year
° as clinically indicated

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## 3. LIST OF ABBREVIATIONS

**RFCA:** radiofrequency catheter ablation;
**AF**: atrial fibrillation
**PVI**: pulmonary veins isolation
**ILR**: implantable loop recorder
**PI**: principal investigator
**CRF**: case report form
**AE**: adverse event
**SAE**: serious adverse event
**SADE:** Serious Adverse Device Effect
**EC:** ethics committee

# 4. INTRODUCTION AND RATIONALE

In the last three decades, radiofrequency catheter ablation (RFCA) has developed from an experimental procedure to a valid and well established treatment option for many patients affected by atrial fibrillation (AF)[2].
Despite improvements in this technology, arrhythmic recurrences are still present and often are linked to electrical gaps in pulmonary veins isolation (PVI). These and other factors have led to research of new technologies. Recently, a new promising technology has been developed for PVI: the laser balloon ablation. The HeartLight Endoscopic Ablation System (CardioFocus, Inc,Marlborough, MA) is designed to achieve PVI with a catheter that includes several unique features including a compliant balloon and a small endoscope, used to aim an adjustable arc of laser energy. Worldwide experiences with laser balloon are growing and a recent meta-analysis on 1188 patients has showed an estimate of 12-month freedom from recurrences of 74%[1]. These data were obtained performing the verification the veins isolation with a mapping catheter positioned within the target PV ostium at the end of the procedure. This additional step may length the procedural and fluoroscopy times, increasing also the risk of complications without proven benefits. In our clinical practice, this additional check of PVI is not performed. In addition, all the available data on the success rate of laser balloon ablation were provided without continuous heart rate monitoring. It is well known that AF recurrences are often asymptomatic and studies on AF ablation efficacy should apply a continuous monitoring approach.
In this observational study, we aim to assess the efficacy at 1-year of AF laser balloon ablation without verification of electrical PVI using implantable loop recorder (ILR) monitoring.

# 5. STUDY OBJECTIVES

### *5.1 Primary*

The purpose of this prospective clinical study is to assess in a patients with paroxysmal or persistent AF the 1-year clinical outcome of the laser balloon ablation without verification of electrical PVI using ILR monitoring.

### *5.2 Secondary*

The Assessment of safety and procedural times of the laser balloon ablation procedure.

# 6. ENDPOINTS

### *6.1 Primary Endpoint*

Success rate at 1-year, defined as:

Free from AF, atrial tachycardia and flutter documented with ILR or Holter ECG monitorwithout antiarrhythmic drugs.

### *6.2 Secondary Endpoint*

- Procedural and 1-year complications related to the ablation procedure.
- Procedural time of the ablation procedure.
- Fluoroscopy time of the ablation procedure.
- Time to first symptomatic AF recurrence.
- Time to first asymptomatic AF recurrence.
- Need for a redo ablation procedure.

- Need for antiarrhythmic drugs.
- AF Burden quantified with ILR/Holter ECG at follow-up visits.

# 7. STUDY DESIGN

### *7.1 Description of the Protocol*

This is a prospective and single-center study. A targeted number of 82 patients suffering from paroxysmal or persistent AF, indicated to undergo catheter ablation will be included. The study will consist of: i) patient enrolment, ii) treatment phase, and iii) 1-year follow-up phase. The duration of the study is expected to be 24 months, from first patient enrolment to last patient follow up.

### *7.2 Number of subjects required to be included in the study*

In a recent meta-analysis including 1188 patients, free from arrhythmic recurrences at 12 months after a single ablative procedure with a laser balloon and without continuous monitoring with ILR was 74%[1].

Assuming that the approach without post-ablative verification of pulmonary vein isolation and continuous monitoring with ILR can lead to a 60% success rate at 12 months, 80 patients are required to have an 80% probability to observe a level of 2-code significance of 0.05 in an exponential model with the log rank test. With an estimated loss of data (patients lost to follow-up, protocol deviations and incomplete data) of 5%, the total number of patients to be enrolled is 82.

### *7.3 Estimated time needed to enrol this subject population*

Subject screening and enrolment will be carried out for approximately 12 months. The study will continue up to 12 months after last patient enrolment, dependent on the rate of enrolment and the regulatory timeline (as applicable).

# 8. SELECTION OF PATIENTS

### *8.1 Number of patients planned*

All patients referred to the Department of Arrhythmology for the management of parosysmal or persistent AF will be considered for eligibility. A subject, who meets all of the inclusion criteria, and none of the exclusion criteria, is eligible to participate in this study.

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented, assigning an identification code linked to their names, alternative identification or contact information.

This log will be kept up to date throughout the clinical study by the principal investigator (PI) or his/her authorized designee. To ensure subject privacy and confidentiality of data this log must be maintained throughout the clinical study at the clinical site.

### *8.2 Inclusion criteria*

To participate in this clinical subject, the subject must meet all of the following inclusion criteria:

- Age between 18 and 85 years
- Paroxysmal or persistent AF

- Patients AF who have indications for the first time ablation procedure according to the ESC / EHRA recommendations (European Society of Cardiology / European Heart Rhythm Association).
- Ability to provide written informed consent for study participation and be willing and able to comply with the study evaluations and follow up schedule

### *8.3 Exclusion criteria*

Subjects are not eligible for clinical study participation if they meet any of the following exclusion criteria:

- Previous AF ablation procedures
- Secondary AF due to other causes
- Hyperthyroidism
- Left ventricular ejection fraction <30%
- NYHA class IV
- Left atrium area > 35 cm2
- Severe disease of cardiac valves
- Contraindication to anticoagulant therapy
- Presence of thrombus in the left atrium
- Myocardial infarction or unstable angina or recent coronary artery bypass (<6 months)
- Thoracic surgery for congenital, valvular or aortic disease
- History of cerebrovascular events
- Pregnancy
- Significant comorbidity, such as cancer, severe kidney failure requiring dialysis, severe obstructive pulmonary disease, cirrhosis, with a life expectancy of less than 2 years
- Contraindications are present as indicated in the "instructions for use" of the devices used

## 9. TREATMENTS

### *9.1 Device used for the ablation procedure*

- HeartLight Endoscopic Ablation System (CardioFocus, Inc, Marlborough, MA)

All devices are CE marked and used according to registered indications and according to normal clinical practice.

### *9.2 Procedures*

The clinical study will be conducted in accordance with the CIP. All parties participating in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

### *9.3 Enrollment visit*

All patients will undergo screening for the inclusion/exclusion criteria outlined in section 8, to determine the patient's eligibility for participation in the study. Once it has been determined that the patient meets eligibility criteria, the PI, or designee, is responsible for obtaining informed consent from each prospective study patient prior to commencement of study procedures. Complete an Enrollment Case Report Form (CRF) and record enrolment information in the hospital records in a timely manner (recommended within 5 days).

If a subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject cannot participate in the study and cannot be enrolled.

In case the subject was already consented to participate in the study, but does not meet inclusion/exclusion criteria, the following actions will be taken.

If study procedure has not occurred:

- Document enrolment information (name of the study, date of consent and inclusion/exclusion) in the hospital records; complete the Enrollment and Withdrawal CRFs. The form must be authorized / approved by the PI or delegated investigator.
  - Inform the subject about the withdrawal.
  - The EC and CA should be notified appropriately about any deviations with regards to obtaining the informed consent.

If study procedure has occurred:

- Document enrolment information (name of the study, date of consent and inclusion/exclusion) in the hospital records; complete the Enrolment and Withdrawal CRFs. The form must be authorized / approved by the PI or delegated investigator.
  - Complete study deviation for inclusion/exclusion not met
  - The EC and CA should be notified appropriately about any deviations with regards to obtaining the informed consent.
  - Subjects will be followed as per physician discretion.

### *9.4 Baseline Visit*

- The following information will be collected at the baseline visit
  - Demographics- include subject's Year of Birth and Gender
  - Physical examination- include subject's height, weight, blood pressure (measurements taken during visit)
  - AF History (first episode, frequency and duration of AF episodes, previous treatment, primary indication for AF ablation)
  - Medical History- indicate subject's risk factors, relevant co-morbidities, previous cardiac procedures
  - Medication (only chronic cardiac related medication)- indicate the drug category the subject is currently taking on a long term base, i.e. no short term medication
  - NYHA classification

- The following activities will be performed at the baseline visit:
  - 12-lead ECG
  - Echocardiogram

Patients will be given a diary for recording AF-related signs/symptoms and instructed to bring it back for follow up visits. A patient number will be assigned, following chronological order.

### *9.5 Laser balloon ablation Procedure*

Selective PV angiography is commonly used prior to positioning of the laser balloon within the target PV ostium. No 'over-the-wire' mechanism is offered, however, an atraumatic soft tip situated at the distal portion of the balloon facilitates safe manoeuvring within the left atrium.
Once in proper position the balloon is filled and continuously flushed with heavy water (deuterium, D2O). Heavy water does not absorb laser energy. The balloon size ~~can~~ be increased in nine

incremental steps from 9 to 35 mm in diameter, depending on the filling pressure within the compliant balloon. Once the balloon is inflated and in proper contact with the opposing tissue, the operator steers the aiming beam to the desired position. A single laser application spans a 30° angle. To ensure a contiguous circular lesion set, adjacent lesions should overlap by 30–50%. Energy delivery can be adjusted from 5.5 W to a maximum of 12 W. Higher energy selection will result in a greater number of acutely isolated PVs following completion of the initial circumferential lesion set. Along the anterior aspect of the septal and lateral PVs power is set to 12 W delivered over 20 s. Along all other locations a maximum power of 10 W for 20 s is used. If perfect sealing between balloon surface and target tissue is not achieved, power should be decreased to 5.5 W delivered over a length of 30 s. Laser ablation may target each PV individually or attempt wide circumferential PVI similar to conventional radiofrequency ablation. However, circumferential isolation should only be attempted if the ipsilateral inferior PV ostium is visualized when targeting the superior PV and vice versa in order to complete the circumferential lesion set at the level of the carina. Since the distance between the right superior and inferior PVs is often greater than between the lateral PVs, circumferential ablation of the septal PVs may only be feasible in a small number of patients. Electrical cardioversion may be performed at the end of the procedure.

Technical information will be recorded in the e-CRF.

- Procedural details
- Duration of ablation
- Sites of ablation
- Substrate characteristics
- Procedural success
- Medications
- AEs and procedure-related complications

## 10. Assessments and procedures

### *10.1 Efficacy*

The primary efficacy endpoint is the freedom from any AF or atrial tachycardia (AT) assessed from the end of the 1 month blanking period to 1 year following the ablation procedure, documented by ILR/ECG Holter monitoring.

Results of the following clinical and instrumental assessments will be recorded.

### *10.2 Clinical assessment methods*

- Demographics and medical history: at baseline;
- Cardiovascular history, AF symptoms as referred by the patient: at all visits
- Concomitant medications: at all visits;
- Adverse events: at all visits

### *10.3 Instrumental evaluations*

- Routine ECG at baseline, post procedure and/or prior to discharge and then at subsequent visits, as clinically indicated;
- Echocardiogram: at baseline, and at all visits;
- 12-lead ECG: at all visits;
- ILR/ECG Holter monitoring as appropriately assessed by the physician at each follow-up;

### *10.4 Safety*

Safety evaluation will rely on all AE/SAEs subsequent to spontaneous reporting, or to detection of clinically relevant abnormalities on physical examinations, vital signs, ECG, and laboratory tests.

Possible AEs associated with ablation procedure

| Cardiac Events | Non-cardiac Events |
|---|---|
| • Abnormal ECG<br>• Angina (chest pain)<br>• Arrhythmia<br>• AV fistula<br>• Complete heart block<br>• Coronary artery injury<br>• Cardiac Perforation<br>• Cardiac Thromboembolism<br>• CHF exacerbation – fluid overload<br>• Component damage to ICD or implantable pacemaker<br>• Death<br>• Dislodgement of implantable cardioverter defibrillator of permanent pacing lead.<br>• Endocarditis<br>• Exacerbation of pre-existing atrial fibrillation<br>• Heart Failure<br>• Hypotension<br>• Inadvertent AV block (complete heart block)<br>• Left atrial / esophageal fistula<br>• Myocardial infarction<br>• Obstruction/perforation/damage of the vascular system<br>• Palpitation<br>• Pericardial effusion/cardiac tamponade<br>• Pericardial effusion without tamponade<br>• Pericarditis<br>• Pulmonary vein dissection<br>• Pulmonary vein stenosis<br>• Pulmonary vein thrombus<br>• Temporary or complete heart block<br>• Unintended (in)complete AV, sinus node, heart block/damage<br>• Vessel wall/valvular damage or insufficiency<br>• Ventricular arrhythmia requiring defibrillation | • Air embolism<br>• Anesthesia reaction<br>• Cerebrovascular accident<br>• High creatinine phosphokinase (CPK)<br>• Infections<br>• Local hematomas / ecchymosis<br>• Laceration<br>• Phrenic nerve damage<br>• Pneumonia<br>• Pneumothorax<br>• Pulmonary edema<br>• Pulmonary embolism<br>• Pulmonary hypertension<br>• Pleural effusion<br>• Pseudoaneurysm<br>• Respiratory depression<br>• Skin burns<br>• Syncope<br>• Transient ischemic attack<br>• Vasovagal reactions |

## 11.PATIENT SAFETY

Definitions: **MEDDEV 2.7/3 December 2010; ISO 14155:2012*

*Adverse Events*

An adverse event (AE) is any un-toward medical occurrence, un-intended disease or injury or any un-toward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons (this is restricted to events related to the investigational medical device) whether or not related to the investigational medical device. This includes events related to the investigational device or the comparator. This includes events related to the procedure involved in the investigational plan.

*Serious Adverse Events*

An event is considered serious when:

- led to a death,
- lead to a serious deterioration in health that either:

1. resulted in a life-threatening illness or injury, or
2. resulted in a permanent impairment of a body structure or a body function, or
3. required in-patient hospitalization or prolongation of existing hospitalization, or
4. resulted in medical or surgical intervention to prevent permanent life threatening illness or permanent impairment to a body structure or a body function,

- led to foetal distress, fetal death or a congenital abnormality or birth defect.

This includes device deficiencies that might have led to a serious adverse event if a) a suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.
A planned hospitalization for pre-existing conditions, or a procedure required by the Clinical Investigational Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

*Device deficiency*
Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.
In the case where a device has failed, the Investigator must make every possible effort to return the device to the fabricant.

*Serious Adverse Device Effect (SADE)*
Adverse device effect that has resulted in any of the consequences characteristics of a serious adverse event.

*Unanticipated Serious Adverse Device Effects (USADE)*:
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
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.

Reporting
Investigators are encouraged to report promptly to the local Ethics Committee:

- any SAE,
- any Investigational Medical Device Deficiency that might have led to a SAE if a) a suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.
- New findings/updates in relation to already reported events

**No later than 48 hours after the event or after being informed about the event.**

Incidents will have to be promptly reported to the local PV officer, according to the post-marketing surveillance/vigilance system (Decreto 15 novembre 2005).

The investigator will also keep a detailed tracking of all adverse events occurred during the study and will deliver the form "REGISTRO EVENTI AVVERSI" to the local Ethics Committee on a monthly basis.

# 12.STUDY PROCEDURES

## *12.1 Screening and inclusion procedures*

Patients fulfilling selection criteria, will be informed of the study and asked for participation. A signed Informed Consent Form for study participation must be obtained by the principal investigator (PI) or designated personnel prior to inclusion in the study.

The following routine assessments will be performed and results recorded:

- informed consent completed and signed
- demographic data (gender, age, ethnic origin)
- medical/surgical history
- 12-lead ECG
- Echocardiogram

Results of the previously performed genetic profiling will also be recorded.
A patient number will be assigned at the inclusion visit, following a chronological order.

## *12.2 Ablation procedure*

Selected technical information will be recorded in the e-CRF.

- Duration of laser ablations
- Sites of ablation
- Substrate characteristics
- Procedural success
- Medications
- AEs and procedure-related complications

## *12.3 Post-Ablation and discharge*

Before hospital discharge, anticoagulation will be prescribed for all patients with warfarin up to 6 months after ablation if they remain in stable sinus rhythm and according to current guidelines. Antiarrhythmic medications will also be prescribed, to be continued for the first 3 months and then to be stopped if allowed by the clinical conditions. Subjects will follow the post-procedure according to the standard hospital procedures. The following assessments will be performed and results recorded in the e-CRF:

- Record of AE/SAEs
- 12-lead ECG
- Record of medications prescribed at discharge

## *12.4 ILR implantation*

As standard practice, ILR which will be implanted one month (± 15 days) after the ablation procedure.

## *12.5 Scheduled Follow-ups*

3-Month visit (± 15 days):

- 12-lead ECG •Echocardiogram
- Assessment of AF recurrence by ILR interrogation or Holter ECG
- Record AE/SAEs

- Record of concomitant medications or interventions (if any)

Antiarrythmic medications history.

6-Month visit (± 15 days):
- Assessment of AF recurrence by ILR interrogation or Holter ECG
- 12-lead ECG
- Echocardiogram
- Verification of signs/symptoms from patient daily diary
- Record AE/SAEs
- Record of concomitant medications or interventions (if any)

Anticoagulants may be stopped at this visit.

12-Month visit (± 15 days):
- 12-lead ECG
- Echocardiogram
- Assessment of AF recurrence by ILR interrogation or Holter ECG
- Verification of signs/symptoms from patient daily diary
- Record AE/SAEs
- Record of concomitant medications or interventions (if any)

Every attempt should be made to complete the follow up visits within the defined window periods. The final visit is required for all patients and should occur within 12-month time frame following the ablation procedure.

### *12.6 Unscheduled Visits*

An Unscheduled Visit is defined as a patient visit or hospital recovery that is not within the scheduled follow ups.
The visit still needs to be documented by completing the appropriate forms if applicable, AE, Death and/or Withdrawal.

### *12.7 Definition of source data*

All evaluations that are reported in the clinical database must be supported by appropriately signed identified source documentation which may be found in the following:
- Hospitalization record
- Nursing notes
- Physician notes
- Procedure report
- Local laboratory reports
- Instrumental recordings

## 13.STATISTICAL CONSIDERATIONS

In a recent meta-analysis including 1188 patients, free from arrhythmic recurrences at 12 months after a single ablative procedure with a laser balloon and without continuous monitoring with ILR was 74%[1].

Assuming that the approach without post-ablative verification of pulmonary vein isolation and continuous monitoring with ILR/Holter ECG can lead to a 60% success rate at 12 months, 80

patients are required to have an 80% probability to observe a level of 2-code significance of 0.05 in an exponential model with the log rank test. With an estimated loss of data (patients lost to follow-up, protocol deviations and incomplete data) of 5%, the total number of patients to be enrolled is 82.

Descriptive statistics (arithmetic mean, median as indicated, minimum and maximum and standard deviation) will be calculated for quantitative variables. Absolute frequencies and percentages will be obtained for qualitative variables. Summary statistics and 95% confidence intervals will be presented. Unpaired the Student's *t* test will be used to compare continuous variables and with the chi-square test for categorical variables, as appropriate. All tests are two-tailed.
A detailed statistical analysis plan will be finalized before performing the analysis.

## 14.ETHICAL AND REGULATORY STANDARDS

**Ethical principles**
This Clinical Trial will be conducted in accordance with the principles laid down by the18th World Medical Assembly (Helsinki, 1964 and subsequent revisions) and all applicable amendments laid down by the World Medical Assemblies, the ICH guidelines for Good Clinical Practice and ISO 14155:2012 principles, as applicable.

**Laws and regulations**
This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country in which the Clinical Trial is performed, as well as any applicable guidelines.

**Informed consent**
Prior to a patient's participation in the study the written Informed Consent Form for study participation should be signed and personally dated by the patient. A copy of the signed and dated written Informed Consent Form will be provided to the patient.
The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the local Ethics Committee (EC).

**Ethics Committee (EC)**
The Clinical Trial will not start until a copy of this written and dated approval/favourable opinion has been received by the Sponsor.
During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the EC.
A progress report is sent to the EC annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

## 15.STUDY MONITORING

The Investigator(s) undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice. ISO 14155:2012 and the applicable regulatory requirements.
The investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol in an accurate and legible manner.
The Investigator may appoint other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be timely appointed and listed. The Sub-Investigators will be supervised by and under the responsibility of the Investigator.

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, integrity and validity of the data recorded on the Case Report Forms. It is the responsibility of the Investigator to complete the e-CRF in an accurate and timely manner, recording all observations and other data pertinent to the clinical investigation.

## 16.DATA PROTECTION

The patient's personal data which may be included in the database shall be treated in compliance with all applicable laws and regulations;
When archiving or processing personal data pertaining to the patients, all appropriate measures to safeguard and prevent access to this data by any unauthorized third party ~~will~~ be taken.

## 17. PUBLICATIONS AND COMMUNICATIONS

Authors of the main publication will be the investigators of the participating center. The property of the data will be of the Investigators.

## 18.BIBLIOGRAPHIC REFERENCES

1. Reynolds MR, Zheng Q, Doros G. Laser balloon ablation for AF: A systematic review and meta-analysis. J Cardiovasc Electrophysiol. 2018; 29(10):1363-1370.

2. Calkins H, Hindricks G, Cappato R, Kim Y, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen P, Chen S, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, Avila A, Groot NMSN De, Biase L Di, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao H, Verma A, Wilber DJ, Yamane T, Paola AAV De, Raviele A, Saad EB, Satomi K, Martin K. 2017 HRS / EHRA / ECAS / APHRS / SOLAECE expert consensus statement on catheter and surgical ablation of atrial fi brillation : Executive summary. Hear Rhythm. 2017;14:e445–e494. doi: 10.1016/j.hrthm.2017.07.009.