AF-FLOW Registry

A post market, global registry to evaluate the identification of **A**trial **F**ibrillation sources using the Ablamap Electrographic **FLOW** (EGF) Mapping System to guide ablation therapy in patients with Atrial Fibrillation

Sponsor:	Ablacon, Inc.
Business Address:	4800 Wadsworth Blvd, Suite 310 80033 Wheat Ridge, CO USA
Protocol No:	CP-003
Date:	May 3, 2022
Product:	Ablamap® Electrographic Flow Software
Revision Number:	REV A
Sponsor Contact:	Patty Hevey Ablacon, Inc. Patty.hevey@ablacon.com +1.650.222.3666
Principal Investigator:	Kent Nilsson, MD, Piedmont Athens Hospital Atul Verma, MD, Southlake Regional Health Center
Study Management:	Ablacon, Inc.

PROTOCOL SUMMARY

Objective	This post-market global registry will evaluate the ability of the Ablamap® Software to identify atrial fibrillation sources and guide ablation therapy in patients with atrial fibrillation
Test Device	Ablacon Electrographic Flow (EGF) algorithm technology (Ablamap® Software)
Study Design	Post-market, prospective, multi-center, global registry
Planned Subject Sample Size	Up to 100 subjects
No. of Sites	Subjects will be enrolled at up to ten (10) investigational sites in Europe and United States
Primary Efficacy Endpoint	Acute procedure success defined as the ability to successfully ablate AF sources identified by the Ablamap Software
Secondary Efficacy Endpoints	Freedom from documented episodes of AF recurrence following the blanking period (90 days post-ablation) through 12 months
Inclusion Criteria	1. Suitable candidate for intra-cardiac mapping and ablation of arrhythmias. 2. Above eighteen (18) years of age or of legal age to give informed consent specific to state and national law. 3. Subjects with a history of documented symptomatic atrial fibrillation.
Exclusion Criteria	1. Subjects who are not candidates for cardiac ablation procedures. 2. Pregnant or nursing. 3. Presence of anatomic or comorbid conditions, or other medical, social or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or comply with follow-up requirements.

Follow-Up Schedule

	Subject Visit Description	**Timeframe / Visit Window**
Follow-up Visit Schedule	Ablation Procedure	Day 0
	12 Month Follow-Up	365 ± 45 days
	Unscheduled Visits	As needed/necessary for AF recurrences

Table of Contents

PROTOCOL SUMMARY 2

1. INTRODUCTION 5

2.1 Test Device Description 6
2.2 Justification of Trial Design 7
2.3 Indications for Use 7
2.4 Intended Use 7
2.5 Potential Risks and Benefits 7
2.5.1 Anticipated Risks associated with the Ablamap Software 7
2.5.2 Risks Associated with Participation in the Clinical Study 7
2.5.3 Anticipated Benefits 7

3. STUDY PROTOCOL 8

3.1 Objective 8
3.2 Study Endpoints 8
3.3 Study Design 8
3.4 Enrollment/Screen Failures 8
3.5 Subject Follow-up 8
3.6 Statistical Analysis 8

4 SUBJECT SELECTION 9

4.1 Patient Selection-Criteria for Eligibility 9
4.2 Study Inclusion Criteria 10
4.3 Study Exclusion Criteria 10

5 DATA COLLECTION 10

5.1 Informed Consent 10
5.2 Baseline Data 10
5.3 Pre-Procedure Requirements 11
5.4 General Procedural Recommendations 11
5.5 EGF Procedure 11
5.6 Blanking Period 14
5.7 Follow-up Visits 14
5.7.1 12-Month Follow-Up 14
5.8 Schedule of Events 14
5.9 Subjects Lost to Follow-Up 16
5.10 Subject Withdrawals and Discontinuations 16
5.11 Early Termination of Clinical Investigation 16
5.12 Adverse Event Reporting 17
5.13 Assessment of Adverse Event Severity 19

5.14 Relationship to the Device: 20
5.15 Anticipated Adverse Events and Device Effects 20
5.16 Device Deficiencies 20

6 REGULATORY CONSIDERATIONS 20

6.1 Investigator Responsibilities 21
6.2 Confidentiality and Data Protection 21
6.3 Insurance 21
6.4 Protocol Amendments 21
6.5 Study Reports 21
6.6 Monitoring 22

7 PUBLICATION POLICY 22

8 ABBREVIATIONS AND DEFINITIONS 22

8.1 Table of Abbreviations 22

REFERENCES 24

1. INTRODUCTION

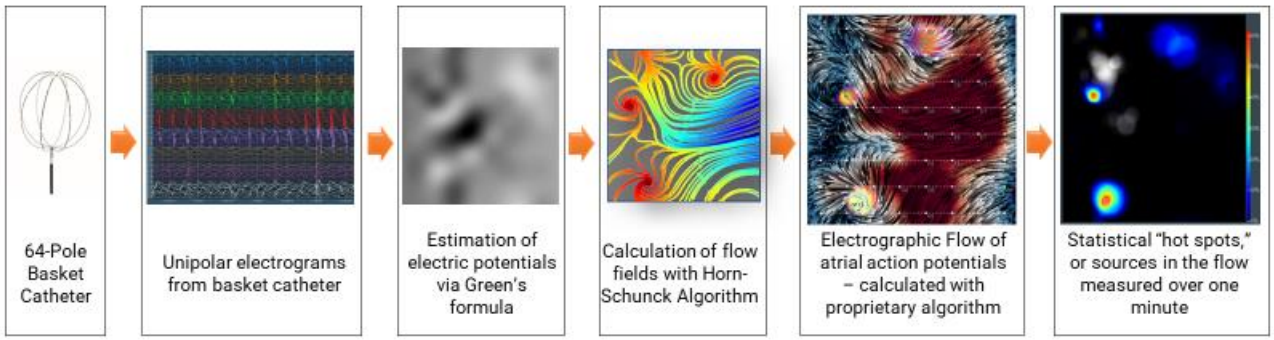
Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with increased mortality, morbidity and impaired quality of life. Catheter ablation has become the standard of care for symptomatic patients with drug-refractory AF and the cornerstone of ablation remains the electrical isolation of the pulmonary veins (pulmonary vein isolation = PVI).[1] For patients with paroxysmal AF, long-term effectiveness of an approach based on PVI as the sole ablation strategy is reported to be 81.6% at 12 months, 73.8% at 24 months, and 68.1% at 36 months post-ablation.[2] However, the success rate of PVI for patients with persistent AF is significantly lower with rates of freedom from AF at 12 months post-ablation ranging from 51 up to 60% regardless of the catheter ablation strategy, addition of antiarrhythmic drugs, use of cryoballoon v. RF ablation, or lesion set performed.[3-6] This ceiling of efficacy in the persistent AF population may be attributable to the complex functional mechanisms of AF contributing to an individual patient's disease state.

Beyond the pulmonary vein triggers, the development and persistence of AF depends upon a localized source—a trigger or driver as well as susceptible substrate, such as re-entrant circuits and or regions of fibrotic atrial myocardium with abnormal conduction properties.[1,7,8] After pulmonary vein isolation has been performed, accurate, enhanced mapping techniques that can localize extra-PV drivers/triggers is needed to further guide the next step in the ablation strategy.

Efforts to hone in on AF mechanisms underlying persistent AF have multiplied and several different methods for identifying these localized sources have been put forth using global or panoramic mapping techniques.[9-12] However, due to the chaotic nature of the intracardiac electrograms (EGMs) characteristic of AF, identifying active focal sources relevant to the initiation and maintenance of AF has remained challenging.

Electrographic Flow (EGF) Mapping (Ablamap® Software, Ablacon, Wheat Ridge, CO) is an innovative technique to create full temporospatial visualizations of organized cardiac action potential flow within the chaotic conduction of AF that can discriminate between active sources of excitation and passive rotations, which do not generate action potentials; and can estimate the average activity of such a source during a time interval such as one minute.[11] It has been shown that only those sources that are generating excitation and that are active more than a quarter of the time are significant predictors for AF recurrence after PVI.[12] Using a 64-electrode basket mapping catheter, the software collects unipolar intracardiac EGMs. These EGMS are then processed using a proprietary algorithm employing Green's energy-optimizing formula to create a smooth landscape of voltage potentials for each sample point in time. An optical flow mapping algorithm is then applied to assemble these snapshots into a continuous recording of the excitation waves' behavior and propagation over time. The software also displays the dominant patterns of the excitation wave propagation recordings as vector flow maps, whose consistency over time can be measured and statistically analyzed (Figure 1):

Figure 1: Methodology of EGF Mapping



Ablacon has recently completed enrollment in the first randomized, controlled, clinical study to evaluate the Ablamap Software (FLOW-AF Study, NCT: NCT04473963). A total of 85 subjects were enrolled across four European centers. All subjects are being followed through twelve months, and the results will be available in late 2022.

The goal of this registry is to continue to evaluate the Electrographic Flow mapping software for identifying AF sources in patients to optimize ablation success in a real-world setting.

2.1 Test Device Description

The Ablamap Software is an electrophysiological mapping software application designed to analyze the flow of excitation in cardiac tissue. The software uses an optical flow algorithm to process recorded files of electrocardiogram (ECG) signals from multiple-electrode mapping catheters (e.g., basket catheters) by transforming the time domain waveform information from all electrodes into space domain information and calculating velocity vectors of the electrographic action potential flow (EGF) for each point in space.

The output is a set of files that graphically depict flow directions (velocity vectors) and sources where the flow is generated. The software discriminates between sources that may be focal or rotational and passive rotations that are not sources; detects spatial and temporal stability of sources; and defines the activity of sources as the percentage of time a source is at its maximum stability.

The Ablamap Software is stand-alone software installed on a standard, commercially available desktop or laptop computer. The software processes ECG data files that have been saved on a USB memory device, the computer, or a data server. The software does not control or interface with any medical device. There is no user or patient contact.

2.2 Justification of Trial Design

The AF-FLOW Registry is a global post-market registry being conducted to collect clinical data to further characterize the performance of the Ablamap Software for its intended use. We also intend to continue to clinically validate the ability of the Ablamap Software to identify AF sources and guide ablation therapy in patients with atrial fibrillation.

2.3 Indications for Use

The Ablamap Software is used to analyze intra-cardiac electrogram (EGM) signals and display results in a visual format for evaluation by a physician in order to assist in the diagnosis of complex cardiac arrhythmias.

2.4 Intended Use

The Ablamap Software is intended to be used during electrophysiology procedures on patients for whom an electrophysiology procedure has been prescribed and only by qualified medical professionals trained in electrophysiology.

The Ablamap Software is CE-marked and FDA 510(k) cleared for use in the EU and United States.

2.5 Potential Risks and Benefits

2.5.1 Anticipated Risks associated with the Ablamap Software

There are no patient or user safety issues or hazards identified for the Ablamap Software in the clinical data analyzed within a comprehensive literature review and the FLOW-AF Clinical Study. Internal data generated as part of the risk analysis of the Ablamap Software indicates there were no patient or user safety issues or hazards identified.

The Ablamap Software Safety Classification per BS EN 62304:2006+A1:2015 is Safety Class A where the hazard probability is *Improbable* and the hazard severity is *Negligible*.

Current market experience shows no evidence to suggest that the Ablamap Software poses any safety issues or any hazards and there are no safety issues or hazards that outweigh the benefits of the system.

2.5.2 Risks Associated with Participation in the Clinical Study

There is no foreseen increased risk to subjects for participating in the clinical study.

2.5.3 Anticipated Benefits

The benefit to the subjects enrolled in this study is the potential for improved judgement by the clinician due to the additional information provided by the Ablamap software. Specifically, the software analyses will guide and support physicians to enable targeted ablation techniques that may improve acute and long-term clinical outcomes.

3. STUDY PROTOCOL

3.1 Objective

The objective of this global post-market registry is to obtain clinical data in order to further characterize the performance of the Ablamap System for its intended use. Specifically, we will evaluate the ability of the Ablamap Electrographic Flow (EGF) System to identify AF sources and guide ablation therapy in patients with atrial fibrillation.

3.2 Study Endpoints

- Primary Efficacy Endpoint: Acute procedure success defined as the ability to successfully ablate AF sources identified by the Ablamap Software.
- Secondary Efficacy Endpoint: Freedom from documented episodes of AF recurrence following the blanking period (90 days post ablation) through 12 months.

3.3 Study Design

The AF-FLOW Registry is a prospective, multi-center global post-market registry that will obtain clinical data in order to characterize the performance of the Ablamap Software for its intended use in a real-world setting. Specifically, we will evaluate the ability of the Ablamap Software to identify AF sources and guide ablation therapy in patients with atrial fibrillation. This registry will enroll up to 100 subjects. Subjects that present with atrial fibrillation and meet inclusion/exclusion criteria will be eligible for enrollment.

3.4 Enrollment/Screen Failures

A subject is considered enrolled after signing the informed consent. All enrolled subjects will then proceed to complete the screening and baseline tests.

3.5 Subject Follow-up

All subjects will be followed per protocol in relation to the date of the index ablation procedure. Follow up will be required at 12 months (±45 days) post index ablation procedure. If a subject presents at any time during the 12-month follow-up period with recurrence of AF, the subject will be eligible for an EGF-guided ablation procedure. The follow-up schedule will remain the same and will not be reset if the patient requires a recurrence procedure.

Note: If any recurrences occur between any study procedures, cardioversion is allowed as often as needed. The number of cardioversions for each subject will be counted and reported.

3.6 Statistical Analysis

The primary efficacy endpoint of this registry is the successful elimination of significant sources of excitation. Target parameter is the activity of the leading source. According to the retrospective data analyzed previously, the critical threshold for significance of a source is an activity of 26%.

Significance of the leading source will be tested in each patient at multiple times, in every procedure performed, in both atria, before and after PVI or PV touch-up and before and after ablation. The effect of targeted ablation will be statistically analyzed by determining the rate of reduction of leading source activity below threshold upon ablation. If an ablation is not successfully reducing the activity or if the location of the leading source changes upon ablation, ablation will be repeated.

The secondary endpoint of the study is freedom from documented episodes of AF recurrence following the blanking period (90 days post ablation) through 12 months.

We will analyze the level of significance of this difference based on the patients with sources above threshold that were successfully ablated and remained AF free versus those patients where no sources or sources below threshold were seen but were not ablated.

Descriptive summary statistics for continuous variables will include the number of subjects, mean, standard deviation or standard error, median, minimum, and maximum. Nominal categorical variables will be summarized using counts and percentages. Ordinal variables may be analyzed as if they were continuously scaled. Subject disposition, the number and percentage of subjects who complete and discontinue as well as reasons for early discontinuation will be presented. Demographic and baseline characteristics will be summarized descriptively.

4 SUBJECT SELECTION

4.1 Patient Selection-Criteria for Eligibility

Subjects enrolled in the AF-FLOW Registry should be selected from the investigators' general patient population with a history of atrial fibrillation that meet eligibility criteria. Patient selection may also be performed by review of the medical records of those subjects who have had prior AF treatment with ablation therapy. Investigators are responsible for screening all potential subjects and selecting those who meet the eligibility criteria for the study.

4.2 Study Inclusion Criteria

Subjects must meet ALL the following criteria:

1. Suitable candidate for intra-cardiac mapping and ablation of arrhythmias.
2. Above eighteen (18) years of age or of legal age to give informed consent specific to state and national law.
3. History of documented symptomatic atrial fibrillation.

4.3 Study Exclusion Criteria

Candidates will be excluded from the study if any of the following apply:

1. Subjects who are not candidates for cardiac ablation procedures.
2. Pregnant or nursing.
3. Presence of anatomic or comorbid conditions, or other medical, social or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or comply with follow-up requirements.

5 DATA COLLECTION

5.1 Informed Consent

All subjects who meet all inclusion criteria and agree to participate in the AF-FLOW Registry will be asked to sign an Informed Consent Form after an explanation of the risks and potential benefits have been provided. 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.

5.2 Baseline Data

Subject source data will be collected per the relevant worksheets, medical reports, procedural reports, lab reports and any other original document in the study subject's chart. In case of electronic source data, accessible without audit trail, printouts have to be produced, verified, and confirmed. Source data will be transferred to CRFs.

After eligible subjects have signed an informed consent form and before the scheduled interventional procedure, subjects will undergo a baseline evaluation. This evaluation may be conducted in accordance with the hospital's standard of care procedures.

The evaluation will include but not limited to the following:

- Medical History and Physical Exam:
  - Subject Demographics
  - Baseline Physical Assessment
    - Height and weight
    - Resting blood pressure
    - Resting heart rate
  - Medical History

- History and documentation of AF
- NYHA score
- CHA_2DS_2-VASc score
- Cardiovascular or other medical history as it pertains to eligibility criteria
- Smoking history

- Medication History
  - Class I-IV AAD history, current doses and/or failure or intolerance
  - Other: Anticoagulants and other cardiac medications

- Baseline Imaging
  - Baseline imaging to rule out LA/LAA thrombus may be done at time of procedure or up to 48 hours prior to the start of any study procedure; however, if any evidence of left atrial thrombus is discovered, the ablation procedure will not be performed at that time. The subject may either be excluded from the study or maintained on oral anticoagulation for an additional period of time (at investigator's discretion). Repeat imaging to rule out thrombi will be required prior to study procedure.
  - A new echocardiogram (transthoracic or transesophageal) should be performed prior to ablation procedure if one has not been performed within six months of the enrollment procedure or if previous data is not available.

5.3 Pre-Procedure Requirements

Subjects should stop all AADs 48 hours prior to the procedure and be appropriately anticoagulated.

Regular amiodarone use should be discontinued at least 1 month prior to the index ablation procedure and not restarted after the ablation procedure.

5.4 General Procedural Recommendations

The ablation procedures (including patient preparation, fluid, ACT, and access site management) should be performed per the institution's standard EP lab protocol. All procedure logistical data, ablation parameters, procedural outcomes, and adverse events, will be recorded throughout the procedure. Prophylactic administration of intravenous diuretics during or after the procedure is allowed and will not be considered an adverse event.

5.5 EGF Procedure

The procedure should begin by verifying the effectiveness and durability of the prior PVI for redo subjects or a complete PVI for de novo subjects. Adenosine or isoproterenol may be administered following the PVI to detect dormant reconnections. If pharmacologic challenge is not used to detect dormant reconnections, a 20-minute wait following the last RF application for PVI should be performed. A commercially available, 64-electrode basket catheter will be introduced into both the right and left atria and unipolar electrograms from the basket catheter will be recorded for one minute each. Recordings are then analyzed with the Ablamap Software. If no sources are seen, or only sources below threshold are detected, the basket should be repositioned until the physician is confident adequate endocardial anatomical coverage has been achieved. If sources above threshold

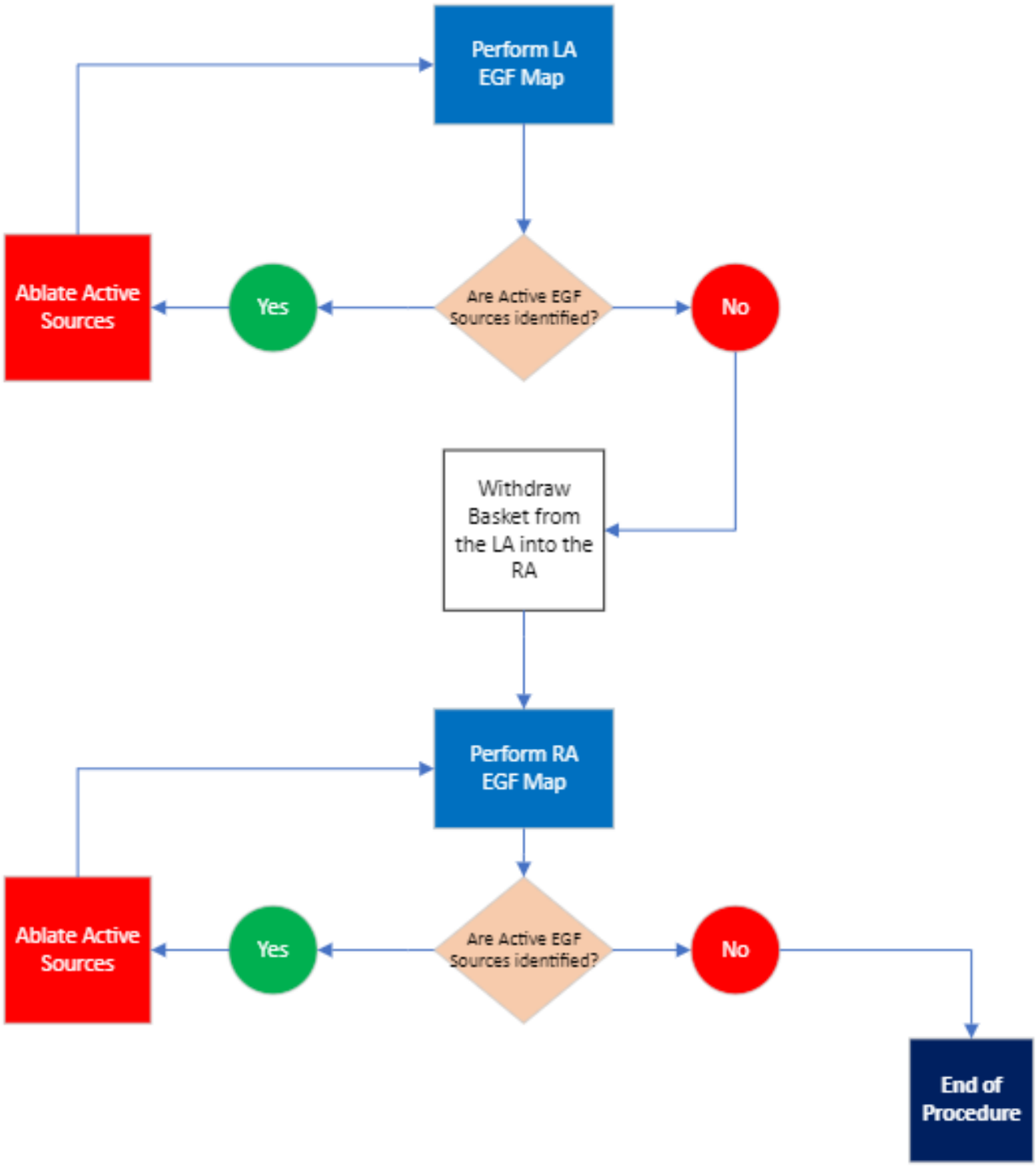
are seen, the patient proceeds to ablation. For those subjects that have no identifiable sources or sources below threshold, the investigator may choose to ablate those subjects per their standard ablation practices.

Once the baseline (i.e., post PVI/PVI touch up) EGF maps are complete, the targeted AF source ablations will be determined according to the results of the EGF analysis using a pre-specified threshold. Ablations should be performed using standard, commercially available ablation catheters/systems. 3D-electroanatomical mapping of both atria will be performed using standard, commercially available mapping systems.

High density bi-atrial voltage mapping using a commercially available multipolar diagnostic mapping catheter during the ablation procedure is required and will be collected for analysis.

EGF mapping should be repeated in the RA and the LA until no further EGF sources above threshold are identified. If AF persists after completion of ablations, cardioversion should be performed.

Figure 2. Workflow for portion of procedure involving EGF-Guided ablation following pulmonary vein isolation



5.6 Blanking Period

The blanking period is the 90-day period following the index ablation procedure. During the blanking period, repeat ablation should not be performed; however, cardioversion may be done at the discretion of the investigator. **If the subject has a recurrence of AF during the blanking period and is placed on AADs, they should be discontinued from the AADs 90 days post ablation.**

5.7 Follow-up Visits

Investigators should follow their standard practices for following subjects post ablation. The AF-FLOW Registry will formally collect baseline demographics, medical history, ablation procedural data and 12-month follow-up visit data.

If a subject returns at any time within the 12-month follow-up period with evidence of AF recurrence, the data will be collected on an Unscheduled Visit CRF.

5.7.1 12-Month Follow-Up

All subjects must be evaluated at twelve months (365 +/- 45 days) after the index ablation procedure.

During this follow-up, the following will be performed:

- Any previously unreported AF recurrences since the index ablation procedure (or cardioversion or repeat ablation procedure for previous AF recurrence).
- Any medication changes (AADs, anticoagulants, and other cardiac medications)
- Perform a 12-lead ECG
- Complete the Study Completion CRF

5.8 Schedule of Events

The tests and measurements to be conducted at baseline, during the treatment procedure, and during follow-up visits are illustrated in the following chart:

Schedule of Events

Schedule of Tests:	**Baseline Assessment**	**Index Ablation Procedure**	**Discharge**	**12 Months** (+/- 45 days)
Informed Consent	X	--	--	--
Eligibility Criteria	X	--	--	--
Pre-ablation Cardiac MRI*	X	--	--	--
High Density Voltage Map(s)	--	X	--	--
Medical History and Demographics	X	--	--	--
Baseline Physical Exam	X	--	--	--
Medication Assessment	X	X	X	X
ECG	X	--	X	X
Adverse Events	--	X	X	X
Procedural Data	--	X	--	--
Protocol Deviations	X	X	X	X

*If performed as part of the investigator's standard of care.

5.9 Subjects Lost to Follow-Up

The investigator will attempt to contact a subject at least three times prior to designating them as lost-to-follow-up subjects; two of these attempts should include attempting to contact subject via registered mail. The investigator will document the date and type of attempted communication and will complete the Study Exit/Completion Form when a subject is confirmed lost to follow-up.

5.10 Subject Withdrawals and Discontinuations

Subjects have the right to withdraw from the clinical investigation at any time and for any reason without prejudice to their future medical care by the investigation team or investigation site. The investigator will ask for the reason for their withdrawal and will record all information regarding the subject discontinuation on the Study Exit/Completion Case Report Form.

5.11 Early Termination of Clinical Investigation

Both the Sponsor and Investigator reserve the right to terminate the clinical investigation at any time.

The Sponsor may suspend or prematurely terminate either a clinical investigation or the entire clinical investigation for significant and documented reasons. Such reasons are as follows:

- If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the EC/IRB or regulatory authorities, the sponsor may suspend the clinical investigation while the risk is assessed. The sponsor may terminate the clinical investigation if an unacceptable risk is confirmed.
- Monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

After review of the clinical safety data, the Sponsor and Investigator may agree to terminate the clinical investigation if necessary. If necessary, and after review and consultation with Principal Investigator, Sponsor will make a final determination on whether to terminate the study.

A principal investigator, EC/IRB, or regulatory authority may suspend or prematurely terminate participation in the clinical study at the investigation sites for which they are responsible.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and sponsor will keep each other informed of any communication received from either the EC/IRB or the regulatory authority.

If, for any reason, the sponsor suspends or prematurely terminates the investigation at an individual investigation site, the sponsor shall inform the responsible regulatory authority as appropriate and ensure that the EC or IRB is notified, either by the principal investigator or by the sponsor. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

If suspension or premature termination occurs:

- The sponsor remains responsible for providing resources to fulfill the obligations from the protocol and existing agreements for following up the subjects enrolled in the clinical investigation, and
- The Principal Investigator or his/her authorized designee will promptly inform the enrolled subjects at his/her investigation site, if appropriate.

5.12 Adverse Event Reporting

An adverse event (AE) is any untoward medical occurrence in a subject. All adverse events are to be reported on the Adverse Event Case Report Form. All adverse events will be documented with the date of occurrence, relatedness to device or procedure, severity, action taken, resolution and any pertinent additional information.

Adverse events will be reported and classified by the investigator from the medical diagnosis, using clinical signs, symptoms or abnormal laboratory values as needed. The investigator will classify the adverse events based on the definitions as follows (ISO 14155:2011).

Term	Definition
Adverse event (AE):	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the test device.
Adverse device effect (ADE):	Adverse event related to the use of a test device.
Serious adverse event (SAE):	Is an adverse event that: a) led to a death, b) led to serious deterioration in the health of the subject, that either resulted in, 1) a life-threatening illness or injury or, 2) a permanent impairment of a body structure or a body function or, 3) an in-patient or prolonged hospitalization or, 4) a medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. ***NOTE**: Planned hospitalization for a pre-existing condition, or a procedure required*

Term	Definition
	by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious adverse device effect (SADE):	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated serious adverse device effect (USADE):	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. **NOTE:** Device deficiencies include malfunctions, use errors, and inadequate labeling.
Device Deficiency:	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.
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 or clinical investigational plan (CIP).
Use 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. **NOTE 1**: User error includes slips, lapses, and mistakes. **NOTE 2:** An unexpected physiological response of the subject does not in itself constitute a use error. [ISO 14971:2012, definition 2.27]

The Investigator will report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports [ISO 14155:2011].

The Investigator will document all Serious Adverse Events (SAEs), including device deficiencies in the study participant's patient file and report it to the Sponsor and/or CRO within 24-hours of knowledge of event. Source data are preferentially immediately transferred to the Adverse Event CRF.

Hospitalizations due to recurrent AF or prolonged hospitalization following procedure to adjust anticoagulation regimen or to administer diuretic medication are not considered AEs for this study. If a subject returns with a recurrence at any time during the study, the incident must be reported on an Unscheduled Visit CRF.

When medical reports (lab results, examinations, etc.) associated with adverse events are submitted to the CRO or Sponsor, all personal subject information (name, address, etc.) MUST be removed or redacted. The redacted materials must be identified only with the Site and Subject's Study Numbers.

The sponsor is responsible for classification and reporting of adverse events and ongoing safety evaluation of the clinical investigation in line with ISO 14155:2011 and regulatory requirements.

The investigator will monitor all AEs until they are resolved, determined to be a chronic condition or the subject is lost to follow-up. The investigator will report all AEs regardless of whether they are anticipated or unanticipated and regardless of classification, seriousness, severity, outcome or causality.

Upon notification of serious adverse events, Sponsor will initiate and complete a review and evaluation of the event within time frames that will maintain reporting compliance with applicable regulatory agencies.

If insufficient information is available to reach a definitive diagnosis, Sponsor will contact the study monitor responsible for the site to request additional confirmatory information, if any. In the event of subject 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 Adverse Event Form. The Investigator will include copies of an autopsy report, if available, and/or a death summary with this form.

5.13 Assessment of Adverse Event Severity

Where the determination of AE severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically-qualified investigator.

The severity of AEs will be graded using the following definitions:

Mild	Awareness of sign, symptom, or event, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity and may warrant intervention
Serious	Incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention

5.14 Relationship to the Device:

Principal Investigators are required to assess whether there is a reasonable possibility that the test device caused or contributed to an AE. Sponsor defines three degrees of relatedness: not related, possible and related to the Test Device. The following definitions will be used to assess the relationship of the Adverse Effect.

Not related	no temporal association, or the cause of the event has been identified; or the device cannot be implicated
Possibly related	temporal association, but other etiologies are likely to be the cause; however, involvement of the device cannot be excluded
Related	temporal association; other etiologies are possible, but unlikely

5.15 Anticipated Adverse Events and Device Effects

The anticipated adverse events and device effects that will occur during this investigation are not different than those risks related to standard catheter ablation procedures. There will be no additional risks to the subjects as a result of using the Ablamap software.

5.16 Device Deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of the test device shall be documented and reported to the Sponsor. For the purposes of this study protocol, the Ablamap software under evaluation will be considered the test device. If a device used during the study procedure (basket catheter, diagnostic catheters, sheaths, etc.) malfunctions at any time, the study site should follow the procedures for returning the product for investigation to the manufacturer of the device. In the unlikely event that the Ablamap software fails, a detailed description of the failure mechanism should be summarized on the Device Deficiency Case Report Form.

6 REGULATORY CONSIDERATIONS

This study will be conducted in conformity with the ethical principles stated in the latest version of the Declaration of Helsinki, 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 and FDA 21 CFR parts 50, 54, 56, 812, or the applicable local and international regulations, whichever provide the greater protection of the individual. The clinical investigation plan and other relevant documentation shall be submitted to the appropriate Ethics Committee/IRB for review. The study will not start without the written approval of the Ethics Committee/IRB and, where needed, the Competent Authority approval and after the completion of any other local regulation requirement.

Before commencement of the study, each Investigator must provide the Sponsor with written documentation of Ethics Committee/IRB approval of both the protocol and the informed consent form, which must comply with all requirements outlined by the Sponsor. This approval must refer to the informed consent form and the study by title and the protocol number as given by Sponsor. Any Investigator who is also a member of the Ethics Committee and/or IRB is not to participate in the protocol approval decision. This non-participation must be noted in the approval letter.

6.1 Investigator Responsibilities

The role of the Investigators is to implement the day-to-day conduct of this clinical investigation as well as to ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation in accordance with ISO 14155:2011 for the conduct of clinical investigations of medical devices. The Investigators shall be qualified by education, training and experience for the proper conduct of this clinical investigation. The investigative site will have the required number of eligible subjects, a qualified investigation team, and adequate facilities for the foreseen duration of this study. The Investigators will provide the sponsor copies of all communication with the EC/IRB, will perform safety reporting to both the sponsor and the EC/IRB according to EC/IRB requirements and to this clinical investigational plan and will promptly report to the EC/IRB any deviations that affect the right, safety, or well-being of the subject, or the scientific integrity of the clinical investigation, as required by local regulations. The Investigators shall ensure compliance with the Informed Consent process and with the clinical investigational plan/protocol and will provide adequate medical care to the subjects during and after their participation in the clinical investigation.

6.2 Confidentiality and Data Protection

Health data will be recorded and forwarded to the sponsor of the study, and to participating Ethics Committees, IRBs, as applicable, for evaluation as required. Any information that is obtained in connection with this study that can be identified with the subjects will remain confidential. data that may be published in scientific journals will not reveal the identity of the study participants.

6.3 Insurance

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

6.4 Protocol Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Any modifications to the Clinical Protocol shall be agreed and signed by the investigator(s). The amendment should be submitted to their respective EC/IRB that originally approved the investigation. A summary explaining the changes, the rationale for changes and other documents will be provided in accordance with applicable requirements, to ECs/IRBs and regulatory authorities. Appropriate approvals of the revised protocol must be obtained prior to implementation.

6.5 Study Reports

The study will be considered complete for the purpose of reporting results regarding the primary endpoints after all subjects have completed the 12-month follow up visit. A final study closeout report will be created after the last 12-month follow-up visit is complete; all subjects are exited from the study; all data queries are resolved; and the investigator has signed off on the accuracy of the data. The PI will review and sign the document, and Sponsor will supply it to the governing Ethics Committee and to the respective regulatory authorities as applicable. The Sponsor may do

an interim analysis on the study data at a pre-determined time outlined in the data management plan.

6.6 Monitoring

Monitoring will be performed during the study by individuals that are appropriately trained and qualified to assess continued compliance with the protocol and applicable regulations. In addition, the monitor will verify that the study records are adequately maintained, that the data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The investigator/institution guarantees direct access to original source documents by the Sponsor personnel, their designees, and appropriate regulatory authorities.

A protocol-specific Monitoring Plan will describe the frequency and extent of the monitoring, including source documentation verification required for the study. Data will be reviewed for trends in changes in the site compliance, and appropriate corrective and preventive actions as well as corrective action plans, will be developed. This review may trigger increased monitoring frequency and/or implementation of corrective action plans at the site.

Monitors will be selected and assigned by Sponsor's clinical management or personnel authorized to supervise the monitoring program.

7 PUBLICATION POLICY

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 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.

8 ABBREVIATIONS AND DEFINITIONS

8.1 Table of Abbreviations

Abbreviation	Definition
AAD	Antiarrhythmic drugs
AE	Adverse Event
AF	Atrial Fibrillation
EC	Ethics Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
IFU	Instructions for use
IRB	Investigational Review Board

ISO	International Standard Organization
IU	International Unit
LA	Left Atrium
LVEF	Left Ventricular Ejection Fraction
NYHA	New York Heart Association
RA	Right Atrium
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

REFERENCES

1. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275-e444.

2. Knight BP, Novak PG, Sangrigoli R, et al. Long-Term Outcomes After Ablation for Paroxysmal Atrial Fibrillation Using the Second-Generation Cryoballoon: Final Results From STOP AF Post-Approval Study. JACC Clin Electrophysiol 2019;5:306-14.

3. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812-22.

4. Berger WR, Meulendijks ER, Limpens J, et al. Persistent atrial fibrillation: A systematic review and meta-analysis of invasive strategies. Int J Cardiol 2019;278:137-43.

5. Ravi V, Poudyal A, Pulipati P, et al. A systematic review and meta-analysis comparing second-generation cryoballoon and contact force radiofrequency ablation for initial ablation of paroxysmal and persistent atrial fibrillation. J Cardiovasc Electrophysiol 2020;31:2559-71.

6. Clarnette JA, Brooks AG, Mahajan R, et al. Outcomes of persistent and long-standing persistent atrial fibrillation ablation: a systematic review and meta-analysis. Europace 2018;20:f366-f76.

7. Lim HS, Hocini M, Dubois R, et al. Complexity and Distribution of Drivers in Relation to Duration of Persistent Atrial Fibrillation. J Am Coll Cardiol 2017;69:1257-69.

8. Cheniti G, Vlachos K, Pambrun T, et al. Atrial Fibrillation Mechanisms and Implications for Catheter Ablation. Front Physiol 2018;9:1458.

9. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol 2012;60:628-36.

10. Honarbakhsh S, Schilling RJ, Dhillon G, et al. A Novel Mapping System for Panoramic Mapping of the Left Atrium: Application to Detect and Characterize Localized Sources Maintaining Atrial Fibrillation. JACC Clin Electrophysiol 2018;4:124-34.

11. Verma A, Sarkozy A, Skanes A, et al. Characterization and significance of localized sources identified by a novel automated algorithm during mapping of human persistent atrial fibrillation. J Cardiovasc Electrophysiol 2018;29:1480-8.

12. Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. Circulation 2014;130:530-8.