FLOW-AF
Clinical Study Protocol

A randomized, controlled study to evaluate the reliability of the Ablacon Electrographic **FLOW** (EGF) algorithm technology (Ablamap® Software) to identify **AF** sources and guide ablation therapy in patients with persistent atrial fibrillation

Brief Title	FLOW-AF: A Study to Evaluate the Ablacon Electrographic FLOW EGF Technology
Clinicaltrials.gov identifier	NCT04473963
Device Name:	Ablamap® Electrographic Flow Algorithm Technology
Protocol No	CP-001/CP-002
Revision Number	REV C
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Sponsor	Ablacon
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1 PROTOCOL SUMMARY

Objective	The objective of this study is to evaluate the reliability of the Ablacon Electrographic Flow (EGF) algorithm technology (Ablamap® Software) to identify AF sources and guide ablation therapy in patients with persistent atrial fibrillation
Test Device	Ablacon Electrographic Flow Algorithm Technology (Ablamap® Software)
Study Design	The study is a prospective, randomized, controlled multi-center study.
Planned Subject Sample Size	A maximum of 100 subjects will be enrolled in this study.
No. of Sites	Subjects will be enrolled at up to five (5) investigational sites in Europe.
Primary Safety Endpoint	Freedom from serious adverse events (SAEs) related to the procedure through 7 days following the Randomization procedure.
Primary Efficacy Endpoint	Acute procedure success defined as the ability to successfully ablate AF sources identified by the Ablacon EGF algorithm
Secondary Efficacy Endpoints	• Consistency of sources identified by the Ablacon EGF algorithm between the randomization procedure and any applicable subsequent EGF-guided ablation procedures as assessed by remapping of the atria and the algorithm's ability to reproduce sources identified by a previous procedure • Freedom from documented episodes of atrial fibrillation recurrence following the blanking period (90 days post procedure through 12 months). • Total number of EGF source ablations • Total time of EGF source ablations • Total fluoroscopy time and dose • Overall procedure time
Inclusion Criteria	1. Suitable candidate for intra-cardiac mapping and ablation of atrial 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, persistent or longstanding persistent atrial fibrillation $\leq$ 36 months. 4. Subject agrees to comply with study procedures and be available (geographically stable) for follow-up visits for at least 12 months.

<table>
<tr><td></td><td colspan="2">5. Treatment of atrial fibrillation with ablation therapy presenting with recurrent symptoms of AF (not applicable to De Novo subjects)</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="2">1. LA diameter > 5.5 cm.
2. Left ventricular ejection fraction (LVEF) < 35%.
3. Presence of intramural thrombus, tumor or abnormality that precludes vascular access, catheter introduction or manipulation.
4. Coagulopathy, bleeding diathesis or suspected procoagulant state.
5. Known allergies or intolerance to anticoagulant and antiplatelet therapies to be used in conjunction with the study or contrast sensitivity that cannot be adequately pre-treated prior to the ablation procedure.
6. Positive pregnancy test results for female patients of childbearing potential or breast feeding.
7. Acute or chronic medical condition that in the judgment of the investigator would increase risk to the patient or deem the patient inappropriate to participate in the study.
8. Mitral valve stenosis and/or severe mitral regurgitation.
9. Valvular atrial fibrillation.
10. Prosthetic valves.
11. NYHA Class IV.
12. History of MI within 3 months prior to procedure.
13. Atrial septal defect (ASD) or left atrial appendage (LAA) closure device.
14. Atrial fibrillation from a reversible cause (e.g., surgery, hyperthyroidism, sarcoidosis or pericarditis).
15. Life expectancy < 12 months based on medical history or the medical judgement of the investigator.
16. Presence of any transvenous pacing, ICD or CRT leads.</td></tr>
<tr><td rowspan="8">Follow-up Visit Schedule</td><td>Subject Visit Description</td><td>Timeframe / Visit Window</td></tr>
<tr><td>Randomization Procedure</td><td>Day 0</td></tr>
<tr><td>Pre-Discharge</td><td>Prior to discharge from hospital following ablation procedure</td></tr>
<tr><td>7 days Follow-Up (Phone)</td><td>7 ± 3 days</td></tr>
<tr><td>3 Month Follow-Up</td><td>90 ± 15 days</td></tr>
<tr><td>6 Month Follow-Up</td><td>180 ± 30 days</td></tr>
<tr><td>12 Month Follow-up</td><td>365 ± 45 days</td></tr>
<tr><td>Unscheduled Visits</td><td>As needed/necessary</td></tr>
</table>

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 is the electrical isolation of the pulmonary veins (pulmonary vein isolation = PVI).[1] Long-term effectiveness of an approach based on PVI as the sole ablation strategy is reported to be high for patients with paroxysmal AF (81.6% at 12 months, 73.8% at 24 months, and 68.1% at 36 months).[2] However, the success rate of PVI is significantly lower with only up to 51% in patients with persistent AF.[3] It is assumed that this is due to the fact that persistent AF is often driven by focal and reentrant activity in the atrial substrate rather than in the pulmonary veins.[4] Accurate, enhanced mapping techniques that can localize those extra PV sources are essential to identify and guide ablation of these sources independently from PVI.

Narayan, et al., used a 64 pole-basket catheter to map AF using unipolar electrograms recorded in the right and the left atrium to construct spatiotemporal source maps.[5] The technology was called Focal Impulse and Rotor Modulation (FIRM). Compared with patients undergoing conventional AF ablation, FIRM guided ablation initially seemed to be associated with a higher acute success and a better outcome as demonstrated in non-randomized studies. However, in randomized multi-center studies, significant benefit of FIRM guided ablation was not confirmed.[6]

Since Narayan's pioneer work several other systems were developed to invasively map rotational activities: Biosense Webster Carto Finder uses phase mapping applied to 64-pole basket catheter unipolar electrograms to identify rotors in the atrial wall.[7] Acutus medical uses dipole density mapping with a 48-pole non-contact basket catheter to identify sources of excitation; CardioNXT uses small spiral catheters to search for AF-sources based on typical source pattern cross-correlation with coronary sinus catheter signals; Volta Medical detects dispersion of activation maps in bipolar electrogram signals recorded using the PentaRay catheter with five splines and 20 poles.[8,9,10] However, none of these newer mapping systems have demonstrated the clinical relevance of these extra-pulmonary vein sources of excitation in the atrial myocardium over a period longer than a few seconds. As such, the ability to identify and ablate relevant non-pulmonary vein foci/triggers to improve freedom from AF post-ablation has not been achieved to date.

The recently developed Electrographic Flow (EGF) Mapping system (Ablamap® Software, Ablacon, Wheat Ridge, CO) is a technology based on a novel algorithm being able to 1) discriminate between active sources of excitation and passive rotations, which do not generate action potentials; and 2) 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] The EGF system uses a velocity vector matrix created through an optical flow analysis applied on surface voltage movies created using a minimal energy algorithm from endocardial unipolar electrograms. The analysis is conducted with the 64-electrode mapping basket catheter, which was also used for FIRM-guided rotor mapping.

The goal of this clinical trial is to evaluate this novel mapping software for identifying AF sources in humans with persistent AF to optimize ablation success in this challenging and heterogeneous patient population. To date no EGF-guided ablation of AF sources has been performed in a controlled trial.

1.1 Test Device Description

The Ablacon, Inc. 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.

The Ablamap® Software is an innovative AF mapping device compared with current devices on the market in that it can quantify the activity of rotors or focal impulses, which are sources of atrial fibrillation and distinct from passive rotors, which are not. It also identifies focal impulses, which are sources that break across/through the atrium wall. Other system(s) cannot quantitatively analyze active and passive rotations and struggle to consider focal impulses because they do not rotate. The quantitative analysis allows monitoring of AF source behavior during therapy guidance and ultimately verification of successful ablations (Bellmann et al 2019).

1.2 Intended Treatment Population

The Ablamap® Software is intended to treat patients with atrial fibrillation for whom electrophysiology procedures have been prescribed.

2 STUDY PROTOCOL

2.1 Objective

The objective of this study is to evaluate the reliability of the Ablacon Electrographic Flow (EGF) algorithm technology (Ablamap® Software) to identify AF sources and guide ablation therapy in patients with persistent atrial fibrillation.

2.2 Primary Endpoints

The primary endpoint events for this trial to assess the safety and effectiveness of the Ablamap® Software System to guide therapy for the treatment of persistent atrial fibrillation are as follows:

- Primary Safety Endpoint: Freedom from serious adverse events (SAEs) related to the procedure through 7 days following the Randomization procedure.
- Primary Effectiveness Endpoint: Acute procedure success defined as the ability to successfully ablate AF sources identified by the EGF algorithm.

2.3 Secondary Endpoints

- Consistency of sources identified by the Ablacon EGF algorithm between the Randomization procedure and any applicable subsequent EGF-guided ablation procedures
- Freedom from documented episodes of AF recurrence following the blanking period (90 days post-ablation) through 12 months.
- Total number of EGF source ablations
- Total time of EGF source ablations
- Total fluoroscopy time and dose
- Overall procedure time

2.4 Study Design

The FLOW-AF study is a prospective, multi-center study conducted to assess the safety and efficacy of the Ablamap® Software System for patients with a history of persistent atrial fibrillation. This study will enroll up to 100 subjects. Patients that present with persistent atrial fibrillation, meet eligibility, and have had a previous ablation procedure prior to being enrolled in the study will be eligible for enrollment. All subjects must be in AF at the time of the procedure.

2.5 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. If they do not meet the eligibility criteria, they will be exited from the study and will not count towards the treated study population.

2.6 Randomization

A 1:1 blocked randomization scheme stratified by site will be used for randomization. Subjects will be randomized based on the results of the pre-procedure EGF mapping procedure. If the subject has identifiable AF sources above a pre-specified threshold, the subject will be randomized to either: 1) immediate EGF-guided radiofrequency ablation with the Ablamap® Software System; or 2) EGF mapping followed by a cardioversion procedure, if required. If the subject is randomized to no treatment, the investigator may choose to cardiovert the subject prior to ending the procedure. Subjects that have no identifiable sources or sources below the threshold will not be randomized. The investigator may choose to ablate those subjects per their standard ablation practices.

2.7 Statistical Analysis

Continuous variables will be reported as mean ± standard deviation and where appropriate as median ± interquartile range. Continuous variables were compared with unpaired t-test, and proportions were compared with the chi-square test. A two-sided p-value of < .05 was considered to indicate a statistically significant difference. For the secondary effectiveness endpoint of freedom from AF from the 90-day post-procedure blanking period through 12 months of follow-up, the length of time to recurrence of AF in each group was analyzed using Kaplan-Meier curves. Data were managed using Microsoft Excel and statistical analyses calculated using Microsoft Excel or Matlab.

3 SUBJECT SELECTION

3.1 Patient Selection-Criteria for Eligibility

Subjects enrolled in the FLOW-AF Study should be selected from the investigators' general patient population with a history of persistent atrial fibrillation that meet eligibility criteria. Patient selection may also be performed by review of the medical records of those subjects whom 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.

3.1.1 Study Inclusion Criteria

Subjects must have met ALL of 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. Subjects with a history of documented symptomatic, persistent or longstanding AF $\leq$ 36 months.
4. Subject agrees to comply with study procedures and be available (geographically stable) for follow-up visits for at least 12 months
5. Treatment of AF with ablation therapy presenting with recurrent symptoms of AF (not applicable to De Novo subjects).

3.1.2 Study Exclusion Criteria

Candidates were excluded from the study if any of the following applied:

- LA diameter > 5.5 cm.
- Left ventricular ejection fraction (LVEF) < 35%
- Presence of intramural thrombus, tumor or abnormality that precludes vascular access, catheter introduction or manipulation
- Coagulopathy, bleeding diathesis or suspected procoagulant state
- Known allergies or intolerance to anticoagulant and antiplatelet therapies to be used in conjunction with the study or contrast sensitivity that cannot be adequately pre-treated prior to the ablation procedure

- Positive pregnancy test results for female patients of childbearing potential or breast feeding
- Acute or chronic medical condition that in the judgment of the investigator would increase risk to the patient or deem the patient inappropriate to participate in the study
- Mitral valve stenosis and/or severe mitral regurgitation
- Valvular AF
- Prosthetic valves
- NYHA Class IV
- History of MI within 3 months prior to procedure
- ASD or LAA closure device.
- AF from a reversible cause (e.g., surgery, hyperthyroidism, sarcoidosis or pericarditis)
- Life expectancy < 12 months based on medical history or the medical judgement of the investigator
- Presence of any transvenous pacing ICD or CRT leads.

3.2 Study Assessments

The tests and measurements that were conducted at baseline, during the treatment procedure, and during follow-up visits are illustrated in **Table 1.**

Table 1. Study Assessments

Study Assessment	Baseline Assessment	Randomi-zation Procedure	Discharge	7 Days (+/-3 Days)	3 Months (+/- 15 Days)	6 Months (+/- 30 Days)	12 Months (+/- 45 Days)
Informed Consent	X	--	--	--	--	--	--
Eligibility Criteria	X	--	--	--	--	--	--
Medical history and Demographics	X	--	--	--	--	--	--
Baseline Physical	X	--					
Medication Assessment	X	X	X	X	X	X	X
12-lead ECG	X	--	X		X	X	X

Study Assessment	Baseline Assessment	Randomi-zation Procedure	Discharge	7 Days (+/-3 Days)	3 Months (+/- 15 Days)	6 Months (+/- 30 Days)	12 Months (+/- 45 Days)
Inclusion/exclusion	X	--	--	--	--	--	--
Holter Monitor						X	X
Adverse Events	--	X	X	X	X	X	X
Procedural Data	--	X	--	--	--	--	--
Protocol Deviations	X	X	X	X	X	X	X

3.3 Subject 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 lost to follow-up.

3.4 Subject Withdrawals and Discontinuation

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.

A subject may be withdrawn from the clinical investigation for the following reasons:

- Subjects may choose to withdraw from the clinical investigation under the terms of the Declaration of Helsinki and their consent documentation without having to give a reason;
- Any unanticipated adverse reaction which is, in the opinion of the Investigator, related to the treatment and will endanger the well-being of the subject if treatment is continued;
- Development of any intercurrent illness(es), infection or condition(s) that might interfere with the Clinical Investigational Plan;
- Non-compliance with the clinical investigation procedures deemed by the Investigator to be sufficient to cause discontinuation;
- Any problem deemed by the Investigator to be sufficient to cause discontinuation.

Investigator will treat all subjects discontinued from the investigation due to an unanticipated adverse reaction, directly related to the investigation, until the reaction resolves.

3.5 Ethics

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 (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. The clinical investigation plan and other relevant documentation shall be submitted to the appropriate Ethics Committee for review. In countries in which additional requirements apply (e.g., notification to, or approval from the Competent Authority), the study may start only after all regulatory requirements are fulfilled.

3.6 Regulatory Considerations

The study will be reviewed by the relevant Ethics Committees, and by the relevant Competent Authority, as applicable. The study will not start without the written approval of the Ethics Committee and, where needed, the Competent Authority approval and after the completion of any other local regulation requirement.

3.7 Confidentiality and Data Protection

Health data will be recorded and forwarded to the sponsor of the study, and to participating Ethics Committees 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.

4 ABBREVIATIONS AND DEFINITIONS

4.1 Table of Abbreviations

Abbreviation	Definition
AF	Atrial Fibrillation
CA	Competent Authority
EC	Ethics Committee
EP	Electrophysiologist
ICF	Informed Consent Form
IFU	Instructions for use
IV	Intra-venous
LA	Left Atrium
LVEF	Left Ventricular Ejection Fraction
NYHA	New York Heart Association
RA	Right Atrium

SAE	Serious Adverse Event

5 REFERENCES

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