

The Tailored-AF trial

Tailored vs Anatomical Ablation Strategy for
Persistent **A**trial **F**ibrillation


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The Tailored-AF trial

CLINICAL INVESTIGATION PLAN

TITLE OF THE STUDY	<u>Tailored</u> vs Anatomical Ablation Strategy for Persistent <u>AF</u>
CIP No.	CL IPL-01-002
TYPE OF STUDY	Interventional, prospective, randomized, controlled, two-arm, multicenter clinical investigation
SPONSOR	Volta Medical 65 Avenue Jules Cantini 13006 Marseille, FRANCE
COORDINATING INVESTIGATOR	Prof. Isabel DEISENHOFER German Heart Centre Munich Lazarettstraße 36 80636 Munich, GERMANY
CONTRACT RESEARCH ORGANIZATION	LABCORP Medical Device and Diagnostic Solutions




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ABBREVIATIONS

AAD	Antiarrhythmic Drug
AE	Adverse Event
AF	Atrial Fibrillation
ANSM	French National Agency for Medicines and Health Products Safety
AT	Atrial Tachycardia
AV	Atrio-Ventricular
BMI	Body Mass Index
CFAE	Complex Fractionated Atrial Electrograms
CIP	Clinical Investigation Plan
CNIL	French National Commission for Data Protection and Liberties
CPP	Committee for the Protection of Persons – French Ethics Committee
CRA	Clinical Research Associate
CRO	Contract Research Organization
CS	Coronary Sinus
CTI	Cavo-Tricuspid Isthmus
DC	Direct-Current
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGM	Intracardiac Electrogram
EP	Electrophysiology/Electrophysiologist
FU	Follow-up
GCP	Good Clinical Practices
IB	Investigator's Brochure
IRB	Institutional Review Board
LA	Left Atrial/Atrium
LVEF	Left Ventricular Ejection Fraction
NOAC	Non-vitamin K antagonist oral anticoagulants
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention

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PV	Pulmonary Vein
PVI	Pulmonary Veins Isolation
QoL	Quality-of-Life
RA	Right Atrial/Atrium
RAA	Right Atrial Appendage
RF	Radiofrequency
SR	Sinus Rhythm
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TTM	Trans Telephonic event Monitor

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SYNOPSIS OF THE STUDY

Title of the Study:	<u>Tailored</u> vs Anatomical Ablation Strategy for Persistent <u>AF</u>
CIP No.:	CLIPL-01-002
Design of the Study:	Interventional, prospective, randomized, controlled, two-arm, multicenter clinical investigation
Sponsor:	Volta Medical 65 Avenue Jules Cantini 13006 Marseille, FRANCE
Coordinating Investigator:	Prof. Isabel DEISENHOFER German Heart Centre Munich Lazarettstraße 36 80636 Munich, GERMANY
Contract Research Organization:	LABCORP, Medical Device and Diagnostic Solutions
Justification / Context:	Atrial Fibrillation (AF) ablation is typically performed in predefined anatomic regions of the left atrium without attempting to identify patient-specific areas of interest. This procedure is referred to as Pulmonary Vein Isolation (PVI). The hypothesis in this Study is that a tailored ablation strategy targeting areas of spatio-temporal dispersion in combination with PVI is superior to an anatomical ablation strategy targeting PVI alone for the treatment of persistent AF.
Primary endpoint:	1. Freedom from documented AF, with or without antiarrhythmic drugs (AADs), 12 months after a single index ablation procedure.
Secondary endpoints:	2. Freedom from documented AF and Atrial Tachycardia (AT), after one or two procedures, with or without AADs, at 12 months 3. Freedom from documented AF/AT, after one procedure, with or without AADs, at 12 months 4. Safety composite endpoint at 12 months: death, cerebrovascular events, or serious treatment-related adverse event
Exploratory endpoints:	5. Freedom from documented AF, after one or two procedures, with or without AADs, at 12 months 6. Freedom from documented AF or AF/AT, after one procedure, or one procedure or more, <u>without AADs</u> , at 12 months 7. Freedom from documented AF or AF/AT, after one procedure, or one procedure or more, <u>without AADs or with previously failed AAD at the same dose</u> , at 12 months 8. Freedom from documented AF or AF/AT, after one procedure, or one procedure or more, with or without AADs, at 12 months, <u>without the use of TTM</u> 9. Freedom from documented <u>symptomatic</u> AF or AF/AT, after one procedure, or one procedure or more, with or without AADs, at 12 months


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	<ol style="list-style-type: none"> 10. Freedom from AF or AF/AT, with or without AADs, 12 months after one procedure, or one procedure or more, for subjects with persistent AF <1 year 11. Freedom from AF or AF/AT, with or without AADs, 12 months after one procedure, or one procedure or more, for subjects with AF ≥ 6 months (including long-standing persistent AF) 12. Estimated AF or AF/AT burden, with or without AADs, after one procedure, or one procedure or more 13. Quality of life measurements (SF-36 and AFEQT) at baseline, 3, 6 and 12 months post-index procedure 14. Incidence of peri-procedural complications including stroke, PV stenosis, cardiac perforation, esophageal injury, and death 15. Acute AF termination rate by ablation 16. Rate of conversion to sinus rhythm by ablation 17. Ablation procedure duration 18. Fluoroscopy time and dose 19. Mapping time 20. Radiofrequency (RF) time to terminate AF 21. Total RF time 22. Total delivered energy (mean power x RF duration) 23. Total delivered energy (mean power x RF duration) / biatrial surface 24. Ablation surface area to terminate AF 25. Total ablation surface area 26. Blinded baseline Voltage maps before ablation 27. TTM compliance (% of transmissions expected vs received at each week post index procedure) 28. Assessment of blind maintenance per group
Inclusion criteria:	<ol style="list-style-type: none"> 1. Patients 18 years of age or older candidates for a first AF ablation 2. Symptomatic AF, refractory to at least one antiarrhythmic medication 3. Persistent or long-standing persistent AF with <u>documentation of</u> (ECG, Holter, physician's letter): <ul style="list-style-type: none"> • AF duration of ≥ 3 months and ≤ 5 years (≥ 3 months and < 1 year in the United States) or • 1 effective cardioversion followed by AF recurrence lasting ≥ 3 months 4. Continuous anticoagulation with warfarin (INR 2-3) or NOAC for > 4 weeks prior to ablation 5. Patients must be able and willing to provide written informed consent to participate in the clinical trial <p>At least 60% of patients (224 patients) in persistent AF ≥ 6 months including at least 15% (56 patients) of long-standing persistent AF ≥ 12 months</p>


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Exclusion criteria:

1. Paroxysmal and short-standing AF < 3 months
2. Long-standing persistent AF > 5 years (≥ 1 year in the United States)
3. ≥ 2 previous ineffective cardioversion sessions in case of undetermined AF duration
4. Severe obesity (BMI > 40)
5. Very dilated Left Atrium (LA) (e.g. LA diameter > 60mm and/or LA surface > 40 cm² determined by 2D echocardiography)
6. Patients with AF secondary to an obvious reversible cause
7. Inadequate anticoagulation as defined in the inclusion criteria
8. LA thrombus on Transesophageal Echocardiography (TEE)* or CT Scan prior to procedure
9. Contraindications to anticoagulation (heparin, warfarin or NOAC)
10. Patients who are or may potentially be pregnant
11. Previous surgical or catheter ablation for AF
12. Any cardiac surgery within the past 2 months (60 days) (includes PCI)
13. Myocardial infarction within the past 2 months (60 days)
14. Previous AV valve surgery
15. History of blood clotting or bleeding abnormalities
16. Documented arterial thromboembolic event (including TIA) within the past 12 months (365 days)
17. Rheumatic Heart Disease
18. Chronic severe Heart Failure (NYHA functional class IV and/or LVEF < 25%)
19. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months (365 days)
20. Unstable angina within the past month
21. Acute illness or active systemic infection or sepsis
22. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause
23. Diagnosed atrial myxoma
24. Significant severe pulmonary disease, (e.g. patients with restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease in GOLD stage IV) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms (e.g. unstable or untreated sleep apnea)
25. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment
26. Enrollment in an investigational study evaluating another device, biologic, or drug
27. Presence of intramural thrombus, tumor or other abnormality or condition that precludes vascular access, or manipulation of the catheter
28. Life expectancy or other disease processes likely to limit survival to less than 12 months
29. Acute Covid-19 infection (fever and/or biological inflammatory syndrome, and positive test documented)

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	* Only TEE is acceptable in the United States to screen for LA thrombus. If a subject cannot have a TEE performed, then intracardiac echocardiography at the beginning of the procedure to screen for LA thrombus is acceptable.
Number of patients to be included:	Approximately 374 patients (187 in each group) (Up to 80 patients in the US)
Estimated duration of the Study:	<ul style="list-style-type: none"> - Study set-up: 4 months - Inclusion phase: 22 months - Patients follow-up: 12 months - Database lock, analysis, and close-out: 3 months - Total duration of the Study: 41 months
Duration of patient's participation in the Study:	Up to 16 months (from enrollment to end of follow-up)

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I – RATIONALE

Introduction

During the past 20 years, atrial fibrillation (AF) has become a major public health problem. AF is the most common arrhythmia in adults affecting about 10 million patients in the European Union alone.¹⁻³ AF is associated with significant morbidity and mortality, a decreased quality of life and contributes to increasing healthcare costs in Western countries.⁴ Still, state-of-the-art AF management remains largely sub-optimal. With current therapeutic approaches, it is estimated that only half of the patients with drug-refractory AF will ever be cured from the disease.⁵ One of the main bottlenecks to improving AF management is the difficulty to durably terminate the arrhythmia and prevent its re-occurrence. In recent years, intense research has enabled the development of an interventional approach to curing AF, named as catheter ablation. Ablation consists of introducing catheters within the heart and delivering tissue-modifying energies in selected sub-regions. Ablation has generated a lot of hope in patients and providers, but its long-term success rate (~50%) remains deceptive, especially for patients with persistent AF.⁵


While various ablation strategies have been suggested with heterogeneous results,⁵⁻¹¹ pulmonary vein isolation (PVI) has emerged as the cornerstone approach.¹²⁻¹⁴ The clinical efficacy of PVI for controlling AF, however, is limited by arrhythmia recurrences due to PV reconnection and/or non-PV triggers. Thus, PVI may not be sufficient to treat all types of AF patients. Multiple works have suggested that the success rate of an ablation procedure could be improved if a sub-set of intra-cardiac electrograms could be identified and targeted.¹⁵⁻²¹ Such approaches, coined as electrogram-based ablation, require sophisticated skills or, alternatively, analytical software to precisely identify the electrograms of interest. Previous research has pointed towards the usefulness of recognizing and targeting multipolar intra-cardiac electrograms exhibiting spatio-temporal dispersion. Specifically, it was demonstrated that the ability to identify dispersed intra-cardiac electrograms (EGMs) could be key to ablation success.^{20,21}

Background studies

The Substrate HD study (ClinicalTrials.gov Identifier: NCT02093949) published in the Journal of the American College of Cardiology in 2017 described the visual criteria that may be used to identify intra-cardiac electrograms exhibiting spatio-temporal dispersion.²¹ Also, this work presented preliminary findings supporting that the targeted ablation of dispersed electrograms may represent an efficacious approach for patients with AF.

Electrogram-based ablation procedure success relies on operators' experience and skills at deciphering multiple tracks-signals while at the same time manipulating intra-cardiac catheters with millimeter precision. The level of dispersed EGMs complexity is such that several years of experience are required to reliably analyze dispersed EGMs. Multiple innovative solutions have been developed to facilitate EGM analysis during AF ablation. For example, the module CARTO CFAEs provides cartographic information based upon measurement of electrogram fractionation.^{22,23} This type of product, however, represents an analysis of individual per-procedural data sets. Thus, this technology "ignores" the thesaurus of analytical parameters that pertain to previous similar procedures. The development of Volta Medical algorithms, relying on artificial intelligence (AI), represents an attempt at satisfying a medical need for an automatic and reliable detection of dispersed electrograms. The methods rely on conceptualizing a discriminant algorithm, which draws anonymized information from a very large database of intra-cardiac EGMS.

The Ev-AIFib study (ClinicalTrials.gov Identifier: NCT03434964) aimed to evaluate the performance and safety of Volta Medical most advanced software VX1 on 300 patients, 8 sites and 18 operators. It was concluded that VX1 is well suited for real-time detection of spatio-temporal dispersion during an AF/AT ablation procedure. Moreover, VX1 allowed for robust center-to-center standardization of acute and long-term ablation outcomes after electrogram-based ablation of persistent AF.²⁴

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Objective

In this study, our objective is to demonstrate that a tailored ablation strategy targeting areas exhibiting spatio-temporal dispersion in association with PVI, is superior to an anatomical probabilistic ablation strategy targeting PVI alone for the treatment of persistent AF. Electrograms harboring spatio-temporal dispersion will be identified using VX1.

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II – DIAGRAM OF THE STUDY

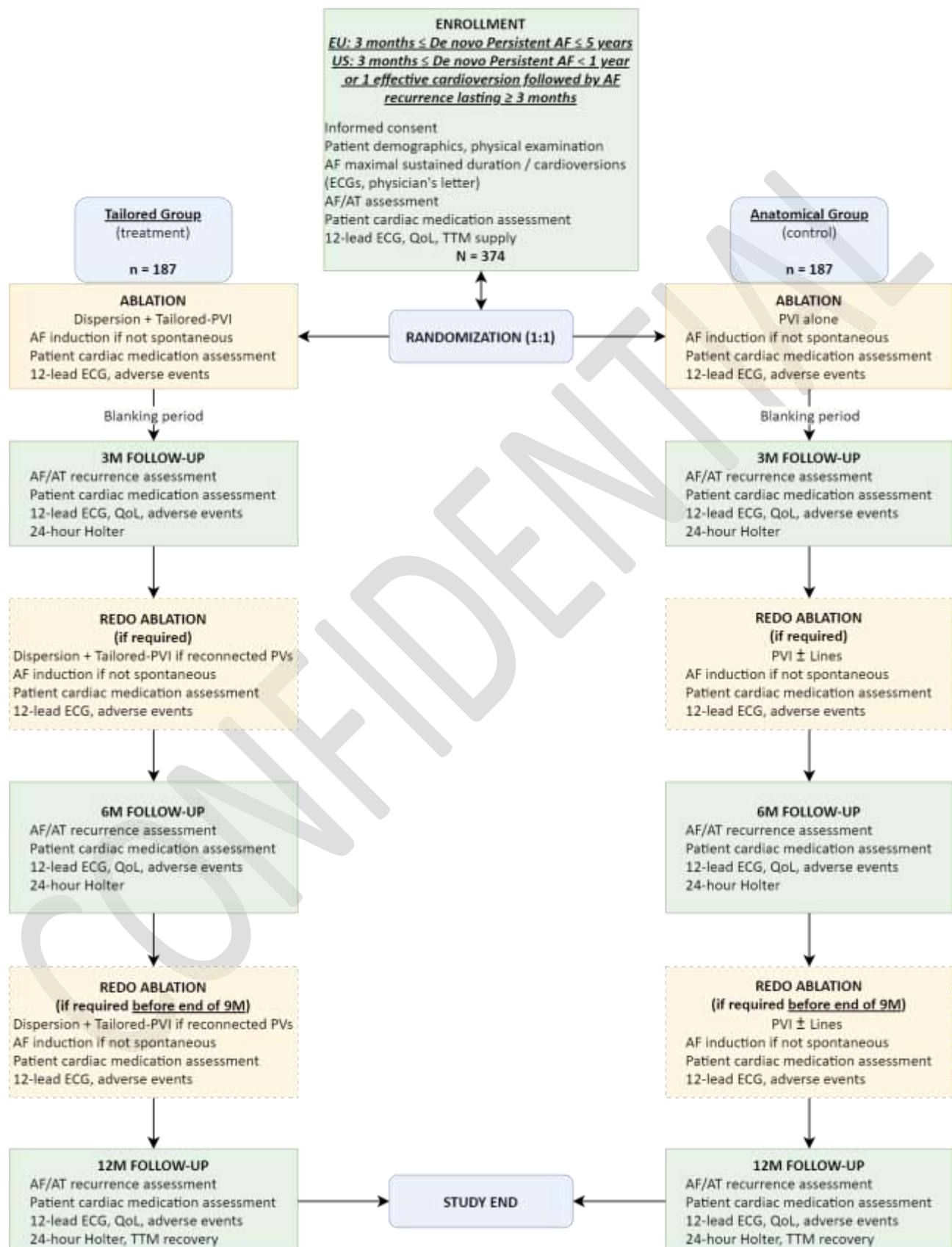


Figure 1: Diagram of the Study

III – DESCRIPTION OF STUDY DEVICES

3.1 – Devices used in this investigation

The following Volta Medical products are required to be used in the investigation:

- VX1 Application (*ref. S001*), version 1.3 or later.
VX1 Application is a class IIa stand-alone software. VX1 Application received initial CE mark on 14 JAN 2020.
- VX1 Hardware (*ref. H001*), version 1.0 or later.
VX1 Hardware is a class I system including a computer with integrated A/D converter with its power supply adapter and detachable power cord, a screen with its power supply adapter and detachable power cord, a data transfer cable, a keyboard and a mouse. VX1 Hardware received CE mark on 09 JUL 2020.

In the United States: A single device, including both software and hardware modules and identified as VX1 (*ref. A001*), is marketed in the USA. VX1 as used in this protocol is investigational in the US.

3.2 – Other devices

Table 1 lists all additional market approved devices that are required to be used in this investigation, and specifies the authorized or compatible brand and manufacturer, if applicable.

Table 1: Authorized other devices


Device	“Anatomical” group (PVI)	“Tailored” group (Dispersion + Tailored-PVI)
3D navigation system	CARTO 3 (Biosense Webster) or EnSite Precision / EnSite X (Abbott) or Rhythmia (Boston Scientific)	
EP recording system	Any EP recording system	Prucka CardioLab (GE) or LABSYSTEM Pro (Boston Scientific)
CS catheter	Any decapolar catheter, regardless of the manufacturer	
Ablation catheter	THERMOCOOL SMARTTOUCH SF (Biosense Webster) or TactiCath (Abbott) or FlexAbility (Abbott) or QDOT MICRO (Biosense Webster) or other RF ablation catheter The use of contact catheter is highly recommended The use of other energies than RF for ablation is not allowed	
Mapping catheter	Any mapping catheter	PENTARAY 2-6-2, Advisor HD Grid, Reflexion HD, IntellaMap Orion

The following market approved devices are allowed to be used in the investigation regardless of the manufacturer:

- Esophageal thermal probe

In Europe: Only CE-marked devices, locally approved and commercially available, will be used within this protocol.

In the United States: Only devices that are FDA cleared/approved and commercially available, will be used. In particular, only the THERMOCOOL SMARTTOUCH SF ablation catheter used with the CARTO 3 navigation system is FDA approved for ablation of persistent AF. Other ablation catheters with compatible navigation systems may be used upon FDA approval for persistent AF indications.

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IV – ENDPOINTS OF THE CLINICAL INVESTIGATION

4.1 – Primary endpoint

The primary endpoint is defined in Table 2.

Table 2: Primary endpoint

Endpoint	Description
Long-term effectiveness primary endpoint	<p>1. Freedom from documented AF*, with or without AADs, 12 months after a single index ablation procedure.</p> <p><i>*Freedom from documented AF is defined as no documented episodes of AF > 30 seconds with conventional non-invasive monitoring (Holters, TTM and 12-lead ECG recordings) between 3 and 12 months after index procedure</i> <i>Difference of freedom from arrhythmia between the arms will be analyzed as comparison of survival distributions of the two arms in order to take into account the time to arrhythmia recurrence and the censored data (cf. 6.5 – Evaluation criteria for primary and secondary endpoints)</i></p>

Possible scenarios that may result in primary endpoint failure:

- A repeat procedure where AF is confirmed during the procedure
- A 30-second or greater episode of AF is documented on a 24-hour Holter prior or subsequent to a follow-up visit
- 30-second of AF on a weekly TTM transmission confirmed by 30-second of AF on same or next week TTM transmission
- A 10-second 12-lead ECG recording confirming AF suggested by either TTM or Holter and subject symptoms

4.2 – Secondary endpoints

Secondary endpoints are defined in Table 3 below.

Table 3: Secondary endpoints

Endpoint	Description
Other long-term effectiveness endpoints	<p>2. Freedom from documented AF/AT*, after one or two procedures, with or without AADs, at 12 months</p> <p>3. Freedom from documented AF/AT*, after one procedure, with or without AADs, at 12 months</p> <p><i>*Freedom from documented AF/AT is defined as no documented episodes of any atrial arrhythmia > 30 seconds with conventional non-invasive monitoring (Holters, TTM and 12-lead ECG recordings) between 3 and 12 months after index procedure</i> <i>Difference of freedom from arrhythmia between the arms will be analyzed as comparison of survival distributions of the two arms in order to take into account the time to arrhythmia recurrence and the censored data (cf. 6.5 – Evaluation criteria for primary and secondary endpoints)</i></p>
Long-term safety endpoint	4. Safety composite endpoint at 12 months: death, cerebrovascular events, or serious treatment-related adverse event

4.3 – Other exploratory endpoints

Exploratory endpoints are defined in Table 4 below.

Table 4: Exploratory endpoints

Endpoint	Description
Other long-term effectiveness endpoints	<p>5. Freedom from documented AF, after one or two procedures, with or without AADs, at 12 months</p> <p>6. Freedom from documented AF or AF/AT, after one procedure, or one procedure or more, without AADs, at 12 months*</p> <p>7. Freedom from documented AF or AF/AT, after one procedure, or one procedure or more, without AADs or with previously failed AAD at the same dose, at 12 months**</p> <p>8. Freedom from documented AF or AF/AT, after one procedure, or one procedure or more, with or without AADs, at 12 months, without the use of TTM†</p> <p>9. Freedom from documented symptomatic AF or AF/AT, after one procedure, or one procedure or more, with or without AADs, at 12 months‡</p> <p>10. Freedom from AF or AF/AT, with or without AADs, 12 months after one procedure, or one procedure or more, for subjects with persistent AF <1 year</p> <p>11. Freedom from AF or AF/AT, with or without AADs, 12 months after one procedure, or one procedure or more, for subjects with AF ≥ 6 months (including long-standing persistent AF)</p> <p>12. Estimated AF or AF/AT burden[#], with or without AADs, after one procedure, or one procedure or more</p> <p><i>*Primary and secondary endpoints 1-4 with no AAD after the blanking period</i> <i>**Primary and secondary endpoints 1-4 with no AAD after the blanking period or with previously failed AAD at the same dose</i> <i>†Primary and secondary endpoints 1-4 with limited non-invasive monitoring (Holters and 12-lead ECG only)</i> <i>‡Primary and secondary endpoints 1-4 considering only documented episodes for which the patient was symptomatic, based on patient declaration (e.g. through TTM recordings annotation) and Quality-Of-Life questionnaire results</i> <i>[#]Post-ablation arrhythmia burden is estimated based on TTM and/or Holter recordings</i></p>
Quality of Life	13. QoL measurements (SF-36 and AFEQT) at baseline, 3, 6 and 12 months post-index procedure
Acute safety endpoint	14. Incidence of peri-procedural complications including stroke, PV stenosis, cardiac perforation, esophageal injury, and death
Acute effectiveness endpoints	<p>15. AF termination rate by ablation*</p> <p>16. Rate of conversion to sinus rhythm by ablation*</p> <p><i>*Correlation between acute effectiveness and long-term effectiveness will be assessed in both arms</i></p>
Additional evaluations	<p>17. Ablation procedure duration</p> <p>18. Fluoroscopy time and dose</p> <p>19. Mapping time</p> <p>20. Radiofrequency (RF) time to terminate AF</p>

	21. Total RF time 22. Total delivered energy (mean power x RF duration) 23. Total delivered energy (mean power x RF duration) / biatrial surface 24. Ablation surface area to terminate AF 25. Total ablation surface area 26. Blinded baseline Voltage maps before ablation* 27. TTM compliance (% of transmissions expected vs received at each week post index procedure) 28. Assessment of blind maintenance per group <i>*Voltage maps must be performed blindly by the operator. In the Tailored arm, the baseline Voltage map is performed during dispersion mapping. In the Anatomical arm, the baseline Voltage map is performed during fast-anatomical mapping.</i>
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V – DESIGN OF THE STUDY

5.1 – General

5.1.1 – Description of the type of clinical investigation

This study concerns a medical device post-CE marking, and has the following characteristics:

- **Interventional:** Enrolled patients will undergo an AF ablation¹
- **Prospective:** Patients are enrolled prior to undergoing an AF ablation
- **Multi-center:** This study will take place in several sites, at least 5 different sites with a maximum number of inclusions per site as defined in this protocol (cf. 6.8 – Minimum and maximum number of subjects to be included for each site). A maximum of 8 sites may participate in the United States.
- **Controlled:** Patients in the Anatomical arm (conventional procedure) constitute the control group
- **Randomized, two-arm:** At enrollment, the patient is randomized 1:1 to one of the arms, Anatomical or Tailored
- **Simple-blinded:** The patient is not aware of the randomization

5.1.2 – Description of measures to be taken to minimize or avoid bias

All patients will be randomized at enrollment in a 1:1 ratio. The patient will not be informed of the randomization.

Special care will be taken to ensure that the patient will be blinded to his/her randomization assignment throughout the study. Patient unblinding should be documented as a non-important deviation.

Moreover, a blind rhythm monitoring is planned: all ECG recordings for long-term effectiveness endpoints (Holter, TTM and 12-lead ECG) will be analyzed and adjudicated blindly by an independent ECG core lab.


5.2 – Subjects and study period

5.2.1 – Inclusion criteria

Patients who meet all the following criteria at the time of enrollment may be included:

1. Patients 18 years of age or older candidates for a first AF ablation

¹ In France, according to the Jardé Law, it is a category 2 interventional study, involving only minimal risks and constraints
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2. Symptomatic AF, refractory to at least one antiarrhythmic medication
3. Persistent or long-standing persistent AF with documentation of (ECG, Holter, physician's letter):
 - AF duration of ≥ 3 months and ≤ 5 years (≥ 3 months and < 1 year in the United States)
 - Or
 - 1 effective² cardioversion followed by AF recurrence lasting ≥ 3 months
4. Continuous anticoagulation with warfarin (INR 2-3) or NOAC for > 4 weeks prior to ablation
5. Patients must be able and willing to provide written informed consent to participate in the clinical trial

At least 60% of patients (224 patients) in persistent AF ≥ 6 months including at least 15% (56 patients) of long-standing persistent AF ≥ 12 months


5.2.2 – Exclusion criteria

Patients who meet any of the following criteria will be excluded from the investigation:

1. Paroxysmal and short-standing AF < 3 months
2. Long-standing persistent AF > 5 years (≥ 1 year in the United States)
3. ≥ 2 previous ineffective³ cardioversion sessions in case of undetermined AF duration
4. Severe obesity (BMI > 40)
5. Very dilated Left Atrium (LA) (e.g. LA diameter > 60 mm and/or LA surface > 40 cm² determined by 2D echocardiography)
6. Patients with AF secondary to an obvious reversible cause
7. Inadequate anticoagulation as defined in the inclusion criteria
8. LA thrombus on Transesophageal Echocardiography (TEE)* or CT Scan prior to procedure
9. Contraindications to anticoagulation (heparin, warfarin or NOAC)
10. Patients who are or may potentially be pregnant
11. Previous surgical or catheter ablation for AF
12. Any cardiac surgery within the past 2 months (60 days) (includes PCI)
13. Myocardial infarction within the past 2 months (60 days)
14. Previous AV valve surgery
15. History of blood clotting or bleeding abnormalities
16. Documented arterial thromboembolic event (including TIA) within the past 12 months (365 days)
17. Rheumatic Heart Disease
18. Chronic severe Heart Failure (NYHA functional class IV and/or LVEF $< 25\%$)
19. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months (365 days)
20. Unstable angina within the past month
21. Acute illness or active systemic infection or sepsis
22. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause
23. Diagnosed atrial myxoma
24. Significant severe pulmonary disease (e.g. patients with restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease in GOLD stage IV) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms (e.g. unstable or untreated sleep apnea)

² An effective cardioversion means that normal sinus rhythm has been restored at the end of the procedure and that the last ECG before discharge shows a sustained sinus rhythm.

³ An ineffective cardioversion means that normal sinus rhythm could not be restored at the end of the procedure or that the last ECG before discharge indicates a reversion to AF.

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25. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment
26. Enrollment in an investigational study evaluating another device, biologic, or drug
27. Presence of intramural thrombus, tumor or other abnormality or condition that precludes vascular access, or manipulation of the catheter
28. Life expectancy or other disease processes likely to limit survival to less than 12 months
29. Acute Covid-19 infection (fever and/or biological inflammatory syndrome, and positive test documented)

*Only TEE is acceptable in the United States to screen for LA thrombus. If a subject cannot have a TEE performed, then intracardiac echocardiography at the beginning of the procedure to screen for LA thrombus is acceptable.

5.2.3 – Criteria and procedures for withdrawal or termination of a subject's participation

A patient's participation ends if any of the following occurs:

- At the end of 12-month follow-up period or if relevant, after resolution of a study-device-related adverse event ongoing at the time of the 12-month follow-up
- If the patient does not undergo an AF catheter ablation
- At any time, in the event of withdrawal of consent or cooperation by the patient
- At any time, if the patient is lost to follow-up
- At any time, in the event of patient's exclusion from the study, required for safety reasons according to the investigator's judgement
- In the event of the patient's death
- At any time, in the event of withdrawal of approval from relevant Ethics Committee or IRB

In each of the above termination cases, the appropriate case report form must be completed to document and justify the end of a patient's participation in the study.

If an adverse effect due to the implementation of the protocol is observed, the study may be suspended at any time by the sponsor.

Premature termination of the study may occur motivated by a general decision (Ethics Committees, IRBs, regulatory Competent Authorities, Data Safety Monitoring Board) for safety reasons related to the use of the device or study procedures.


A site may be terminated for the following reasons: failure to comply with the conditions of the study protocol and/or failure to accurately complete case report forms.

5.2.4 – Expected total duration of the clinical investigation

The clinical investigation will not begin in any center until:

- Approval has been obtained from the relevant Ethics Committees or IRB, including approval from national and/or local Ethics Committees or IRBs as required by current national and/or local laws on the rights, safety, and welfare of human subjects.
- Approval or no objection has been obtained from regulatory Health Authorities, as required by current national and/or local laws on the rights, safety, and welfare of human subjects.
- Liability coverage has been obtained by the sponsor, as required by current national and/or local laws on the rights, safety, and welfare of human subjects.
- Investigator agreement has been obtained from the investigator(s) in the center, as required by the Declaration of Helsinki and national/local laws on the rights, safety, and welfare of human subjects.

The expected total duration of the study is 41 months:

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- 4-month set-up
- 22-month enrollment
- 12-month follow-up
- 3-month database lock, analysis, and close-out

5.2.5 – Expected duration of participation for each subject

Each patient is expected to participate in the study for up to 16 months (cf. Table 8).

The patient's participation in the study begins when patient is determined eligible to participate and he/she has signed the consent form, after having received the appropriate and mandatory information about the study.

The patient's participation in the study ends if any of the situations described in section 5.2.3 – Criteria and procedures for withdrawal or termination of a subject's participation occurs.

5.2.6 – Number of subjects required to be included in the clinical investigation

The number of subjects to be included is 374 patients, i.e. 187 patients in each group (cf. 6.2 – Sample size). The maximum number of subjects to be included in the United States is 80.

5.2.7 – Estimated time required to include this number (i.e. the period of enrollment)

The estimated enrollment period is 22 months.

In case of significant changes in the inclusion phase duration, the relevant Ethics Committees, IRBs, and regulatory Health Authorities, as well as all concerned investigators, will be promptly notified.

At any time, the sponsor may interrupt or suspend enrollment of patients in the study for clinical/safety reasons (such as if an unanticipated adverse effect is observed or suspected) related to the device under investigation. In that case, the relevant Ethics Committees, IRBs, and regulatory Health Authorities, as well as all concerned investigators, will be promptly notified.

In addition to the sponsor, any Ethics Committee, IRBs, or regulatory Health Authorities may also interrupt or suspend enrollment of patients in the study for clinical/safety reasons related to the devices under investigation.

5.3 – Study procedures


5.3.1 – Screening and enrollment

Patients must be informed about the investigation and the potential benefits and risks of the study prior to enrollment. Only those patients who voluntarily provide written consent to participate will be eligible for enrollment.

The following procedures must be conducted **before** inclusion of the patient in the study:

- Evaluate the patient to determine conformance with the inclusion and exclusion criteria. Source data that demonstrate conformance with inclusion criteria should be retained at the investigational site.
- Obtain written informed consent.

Patients are considered enrolled into this clinical study once they have signed an informed consent and met all eligibility criteria. Patients who do not sign an informed consent or do not meet eligibility criteria upon further testing are not eligible and should not be enrolled in the trial.

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After having obtained the informed consent from the patient (and before ablation):

- Fill-out enrollment in appropriate eCRF
- Obtain and record the following data in appropriate eCRF:
 - Patient's demographics
 - Mandatory documentation of the maximum sustained AF duration or number of cardioversions (ECG/physician's letter)
 - Current vitals (physical examination, 12-lead ECG)
 - Routine clinical data including type of AF, LA diameter/surface (echo) or volume (scanner), CHA₂DS₂-VASc score, comorbidities, etc.
 - Patient's current medications
- Provide the patient with Quality-Of-Life questionnaires (SF-36 and AFEQT) and report answers in appropriate eCRF
- For US subjects: A TEE screening will be performed within 48 hours of the ablation procedure unless data from a TEE performed prior to enrollment is available and the TEE was performed within 48 hours of the ablation procedure.
 - If a patient cannot undergo TEE, the use of intracardiac echocardiography at the start of the ablation procedure to exclude LA thrombus is acceptable.

5.3.2 – Randomization

After successful enrollment, the patient will be automatically randomized to one of two arms through the eCRF system: "Anatomical" arm (PVI) or "Tailored" arm (Dispersion + Tailored-PVI). In Europe, randomization will be stratified in order to balance the treatment arms in terms of patients with persistent AF (< 12 months) and long-standing persistent AF (≥ 12 months).

Subjects will not be informed of their randomization assignment.

5.3.3 – Pre-ablation Medication

Treatment with antiarrhythmic medications should be stopped before ablation.

Continuous anticoagulation with warfarin (INR 2-3) or NOAC for > 4 weeks prior to ablation is mandatory. Anticoagulation should not be interrupted before the ablation procedure, unless specifically instructed by the investigator. Only 1 or 2 doses of oral anticoagulation may be interrupted by the investigator.


5.3.4 – Index procedure

The subject will be scheduled to undergo study treatment after the subject has met all inclusion and exclusion criteria, has signed the study informed consent form, has completed the baseline assessments and has been randomized.

AF induction

If the patient does not present in spontaneous sustained AF at the beginning of the procedure, sustained AF must be induced by atrial burst pacing, either with or without the additional infusion/injection of isoproterenol (20 microg/min) ± adenosine (according to site practice).

In the Tailored group, should AF not be inducible or be inducible and non-sustained, the patient will undergo conventional AF ablation per physician discretion. This patient/case will not be considered in the per-protocol analysis.

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Mapping (only for Tailored group)

For the Tailored group, careful biatrial high density dispersion mapping must be performed as the first step of the procedure. A biatrial mapping shorter than 20 minutes is considered incomplete. An incomplete mapping with failure to terminate the AF is considered a deviation of the protocol (cf. X – DEVIATIONS FROM CLINICAL INVESTIGATION PLAN).

Operators must map each region of both atria carefully. Electroanatomic color maps (i.e. voltage maps with minimal interpolation area) or the density of electroanatomic dots on 3D shells can be visually used to verify that the biatrial mapping has been completed. Operators must insist in difficult areas: ridge, anterior Right Superior Pulmonary Vein, area around the transeptal puncture, CS, right septum, area between RA Appendage (RAA) and septum.

Operators should move the mapping catheter slowly and remain in each position for at least 2-3 seconds. If the upper frame of VX1 interface changes from blue to orange/red, the corresponding dipoles must be manually tagged on the 3D shells (white/golden dots respectively – cf. VX1 instructions-for-use). Accuracy and relevance of dispersion regions should be confirmed by the operator by checking EGMs visually. If VX1 identifies an area of dispersed electrograms that the operator does not agree with, this should be documented.

If a dispersion area is detected, the operator must stay and move slowly in this area: a high number of dots is required to define the precise boundaries of the dispersion area.

Intraprocedural anticoagulation

Use of intraprocedural anticoagulation consistent with your standard practice should be used during the index ablation. It is recommended that heparin should be administered prior to or immediately following transeptal puncture during AF catheter ablation procedures and adjusted to achieve and maintain an ACT of at least 300 seconds.

Ablation procedure in the Tailored group

In the Tailored group, the procedure endpoint is sinus rhythm conversion by ablation at dispersion regions mapped during AF and potential subsequent AT(s).

Once mapping is complete:

- 1) The operator starts by ablating all dispersion areas. Tailored-PV-encircling⁴ along dispersion regions is recommended during dispersion areas ablation (cf. Figure 2). Ablation should always be done in a manner to either cover the dispersed electrograms or encircle a large area of dispersed electrograms (cf. Figures 3 and 4)
- 2) The operator then completes the isolation of the 4 PVs
- 3) The electrical connection of the 4 PVs is checked at the end of the procedure according to each site routine practice. Additional perivenous ablation can be performed to electrically disconnect the connected PV(s).

⁴ Tailored-PVI or Tailored-PV-encircling corresponds to PVI or PV-encircling along dispersion areas around the PVs in order to optimize the flow of the procedure.

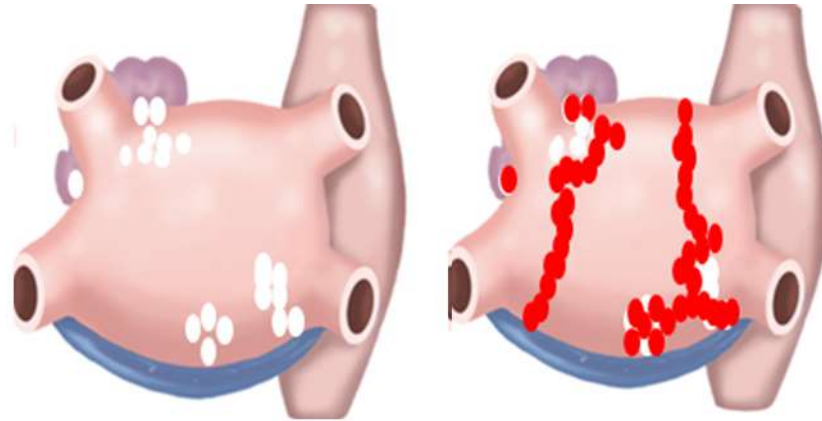


Figure 2: Tailored-PVI after Tailored-PV-encircling

In case of failure to terminate AF after ablation of all dispersion areas, at least one re-mapping/re-ablation is mandated, and two complete re-mappings are recommended. If the patient did not convert to sinus rhythm with ablation, a DC electrical cardioversion is performed.

If sinus rhythm is restored before ablation at all dispersion areas, the completion of the ablation set is mandatory, except in the atrial regions positioned close to the esophagus, phrenic nerve, AV node and/or sinus node. This list is not exhaustive, the operator can identify and document any other potentially hazardous areas for ablation.

When a sustained AT results from the ablation of all dispersion areas, mapping and ablation of AT must be performed with the use of activation maps \pm VX1 \pm pacing maneuvers.

In case of linear ablation performed for macro-reentry (roof, perimitral, cavo-tricuspid isthmus (CTI) flutter), lines should be validated by establishing a post-ablation bidirectional block. The impossibility of performing the line validation must be documented. No line validation is required without documented macro-reentry.

If two ablation areas are close (< 2 cm) or if one ablation area is close (< 2 cm) to an electrically neutral structure (PV, valva), it is recommended to join them in order to reduce the risk of creating areas prone to AT – “Ablate & Connect” strategy (cf. Figure 3).

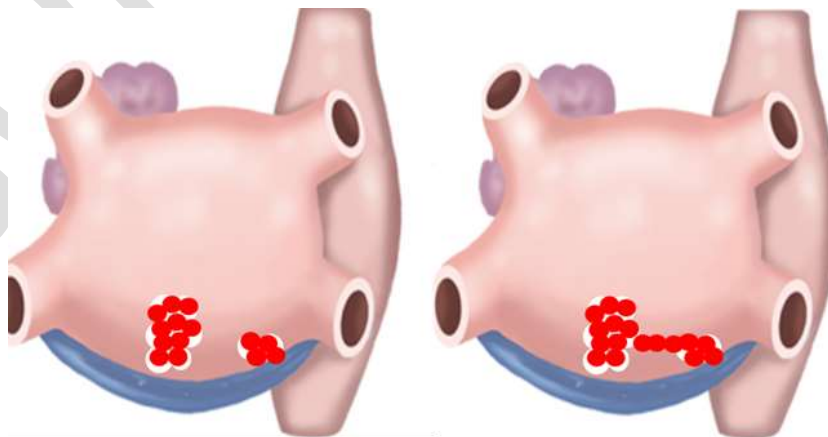



Figure 3: Connection of close dispersion areas (Ablation tags diameter on the 3D shells = 6 mm).

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In the case of a wide and extensive dispersion area, white dots can be encircled so as to electrically isolate each dispersion zone – “Circle & connect” strategy (cf. Figure 4).

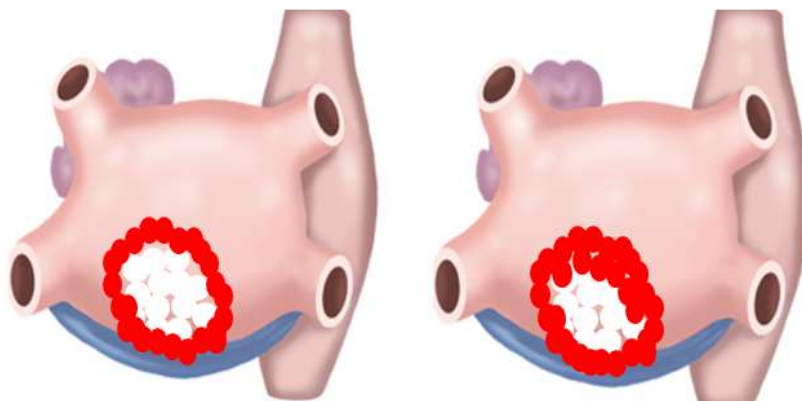


Figure 4: Centripetal ablation

The Tailored ablation protocol is summarized in Figure 5.

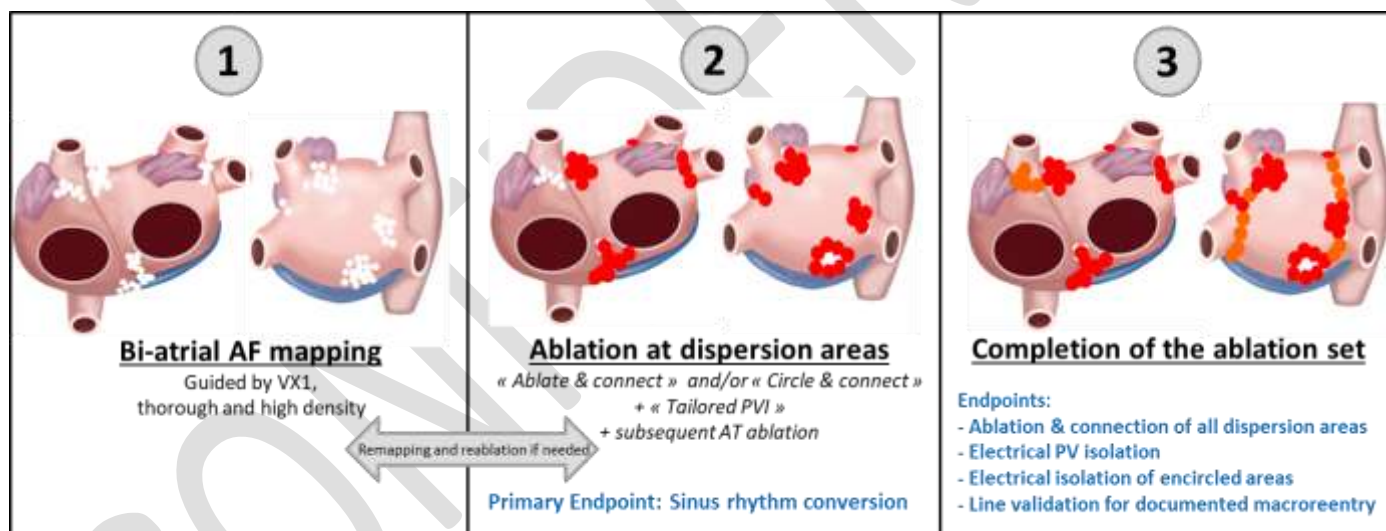


Figure 5: The Tailored protocol

Ablation procedure in the Anatomical group

In the Anatomical group, the procedure endpoint is isolation of all four PVs, documented according to each site routine practice (e.g. bidirectional block with mapping catheter).

The operator creates a contiguous circular lesion around each pulmonary vein antrum (1-2 cm from the ostia) with point-by-point applications of RF energy. If the patient is not converted to sinus rhythm at the end of the procedure, a DC electrical cardioversion must be performed.

No RF applications outside the PV antra are allowed (cf. Figure 6 (b)). RF applications at the carinas are allowed (cf. Figure 6 (a)).

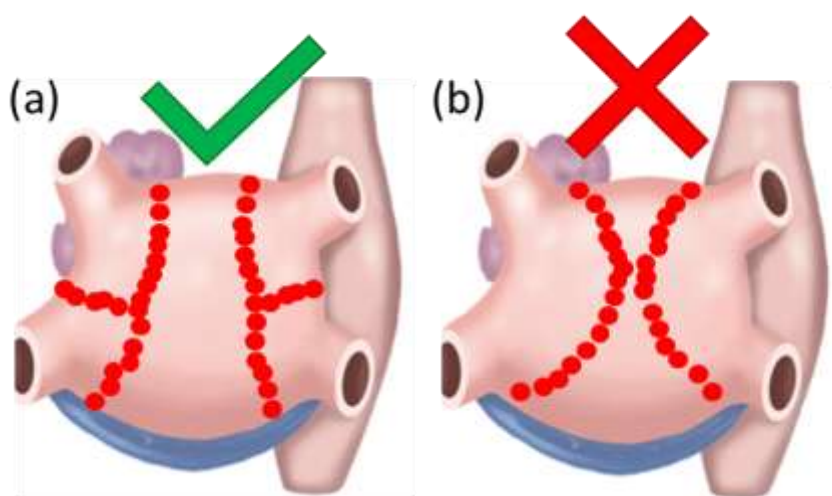


Figure 6: RF applications (a) allowed at the carinas and (b) forbidden outside PV antra

RF application recommendations

Operators will select their contact Force working ranges based on experience during the roll-in cases, review of literature, clinical data. Recommendations: 5-20 g.




High power – short duration RF applications are highly recommended (40-50 watts everywhere except in the CS or close to the esophagus). Table 5 gives recommendations for RF application duration and power. Failure to follow them does not constitute a deviation, as RF application parameters are left to the operator's discretion.

Table 5: RF application duration and power recommendations

Parameter	LA anterior wall / Septum / PV regions / floor	LA ridge / mitral isthmus	LA roof	LA posterior wall	CS	RA	RAA
Power (watts)	40-50	40-50	40-50	25-50	25-30	40-50	40-50
Maximal application time in case of 50 watts applications	30 sec	30 sec	20 sec	15 sec	NA	30 sec	30 sec
Ablation index	500-550	500-550	450-500	350-400	400	450-500	500-550
LSI	5.5-6	5.5-6	5	4	4	5	5.5-6

Number of applications inside/outside these ranges must be quantified (cf. Table 6). The ablation tag diameter should be 6 mm. All tags must be contiguous.

Table 6: Color code for ablation tag

Tag	Ablation index	LSI
Light red 	350-500	4-5
Red 	500-600	5-6.5
Dark red 	>600	>6.5

AT ablation

In case of AT, mapping and ablation of AT should be performed only in the Tailored group. In case of documented history of common flutter or if a subject develops common flutter during the procedure, a cavotricuspid isthmus (CTI) line is recommended regardless of the randomization group.

In case of regularization into a non-common flutter in the Anatomical group, no mapping and ablation should be performed. However, a DC electrical cardioversion must be performed.

Data collection

Table 7: Main data collected during procedure (complete list in eCRF)

Data	Description
Procedure times	Procedure start: Time of insertion of first sheath for vascular access Procedure end: Time of removal of sheaths
Voltage maps	Baseline Voltage maps performed blindly by the operator. In the Tailored arm, the baseline Voltage map is performed during VX1-guided mapping. In the Anatomical arm, the baseline Voltage map is performed during fast-anatomical mapping.
RA/LA volumes	RA/LA volumes in mL without veins
Mapping times	Time of start and end of each AF mapping for Tailored group Time of start and end of fast-anatomical mapping for Anatomical group
Ablation times	Time of start and end of each ablation cycle
Mapping picture	<u>Only for Tailored group</u> Picture of the biatrial shell with electroanatomic dots and VX1 dots before ablation start
Fluoroscopy time and dose	Total fluoroscopy time and dose for the entire procedure
RF times	Total RF ablation time and RF time to AF termination
RF Power	Min, Max and most commonly used RF power value
Ablation surface area	Total ablation surface area and ablation surface area to terminate AF, when the 3D navigation system allows it
Post-ablation picture	Picture of the biatrial shell with ablation tags for both arms and crucial dots for tags for both arms
Crucial dots	Crucial dots* number and location (cf. Figure 7) *Crucial dots = AF/AT termination points or 20-ms cycle length increase

Ablation of VX1-tagged regions	Location and justification of VX1-tagged regions not ablated by the operator
AT data	Number, mechanism, and location (cf. Figure 7) of ATs
Procedure endpoints documentation	Pictures confirming PV electrical isolation, AF termination, SR conversion, lines validation (if applicable)
Medication administration	All cardiac medications administered during the procedure
Devices and equipment	Devices and equipment used during the procedure including diagnostic and ablation catheters, 3D navigation and EP recording systems

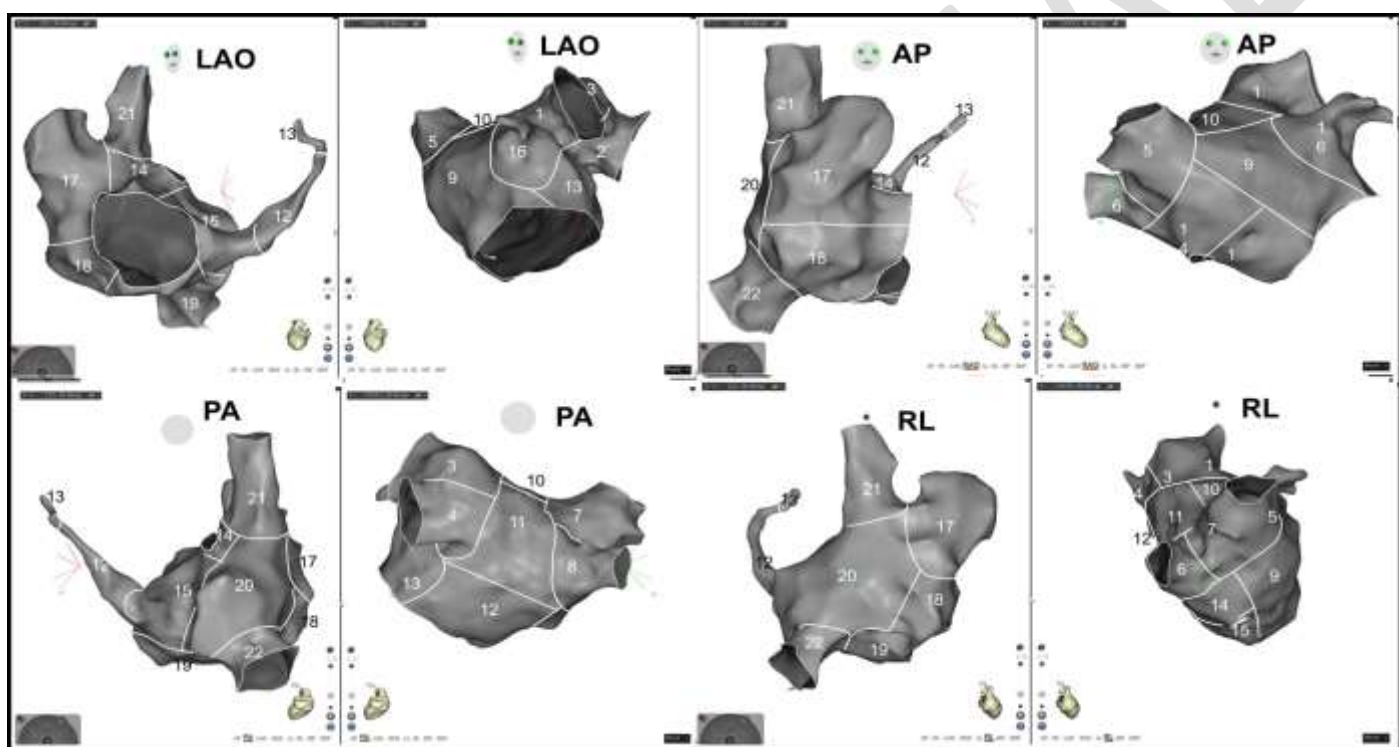



Figure 7 : Bi-atrial segmentation used for characterization of dispersion tagged regions

- | | |
|---|--|
| Region 1: Left superior pulmonary vein anterior antrum – Ridge. | Region 13r: Coronary sinus distal. |
| Region 2: Left superior pulmonary vein inferior antrum-Ridge. | Region 13l: Mitral isthmus. |
| Region 3: Left superior pulmonary vein posterior antrum. | Region 14r: High right atrial septum. |
| Region 4: Left inferior pulmonary vein posterior antrum. | Region 14l: High left atrial septum. |
| Region 5: Right superior pulmonary vein anterior antrum. | Region 15r: Low right atrial septum. |
| Region 6: Right inferior pulmonary vein anterior antrum. | Region 15l: Low left atrial septum. |
| Region 7: Right superior pulmonary vein posterior antrum. | Region 16: Left atrial appendage. |
| Region 8: Right inferior pulmonary vein posterior antrum. | Region 17: Right atrial appendage. |
| Region 9: Anterior wall from mitral annulus to roof. | Region 18: Lateral right atrial appendage. |
| Region 10: Roof. | Region 19: Cavo-tricuspid isthmus. |
| Region 11: Posterior wall. | Region 20: Posterior right atrium. |
| Region 12r: Mid-coronary sinus. | Region 21: Superior cava vein. |
| Region 12l: Left atrial floor. | Region 22: Inferior vena cava |

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Pre-discharge and post-procedure medication

Post-procedure drug therapy will include re-initiation and/or continuation of any pre-procedure cardiac medications and/or prescription of supplemental anti-arrhythmic medications, under the direction of the investigator. All medications will be documented in the appropriate section of the eCRF.

Systemic anticoagulation with warfarin or a NOAC is recommended for at least 2 months after the procedure. Decisions regarding continuation of systemic anticoagulation more than 2 months post ablation should be based on the patient's stroke risk profile and not on the perceived success or failure of the ablation procedure.

The use of antiarrhythmic medications is allowed for the first 3 months (post-ablation blanking period) after the index procedure and discouraged thereafter.

The use of diuretics prophylactically, especially for long procedures regardless of the study arm, is recommended.

5.3.5 – Trans Telephonic event Monitor (TTM)

All patients will receive a portable ECG device (KardiaMobile, AliveCor) that they will keep throughout their participation in the Study. They will be asked to perform one 30-second ECG recording per week, and whenever they have arrhythmia symptoms. All TTM recordings will be automatically uploaded in a secured platform for blind review by the ECG core lab.

5.3.6 – Follow-up period

All patients will be followed-up for 12 months with scheduled in-office visits at 3, 6 and 12 months. A 3-month blanking period will be applied after the index procedure, during which early recurrences of AF/AT will not be counted.

All patients will be required to perform a 24-hour Holter prior or subsequent to each in-office visit at 3, 6 and 12 months post-procedure. The 24-hour Holter recording must be performed within the same time windows as the in-office visit specified in Table 8.


At each in-office visit (3, 6 and 12 months or unscheduled follow-up visit), the following assessments/procedures will be performed:

- Diagnostic 12-lead ECG
- Assessment of Holter report if available (only during scheduled visits)
- QoL questionnaires (only during scheduled visits)
 - It is recommended that QoL questionnaires be completed prior to any other follow-up procedures in order to reduce influencing the subject's responses.
- Concomitant cardiac medications
- Adverse event documentation

At the 12-month visit, a blinding assessment should be done by asking the subject which arm of the study they believe they are in. The subject's response should be recorded.

If AF and/or AT recurrences are observed during follow-up, further treatment shall be at the discretion of the physician (e.g. drugs or re-ablation or cardioversion). Re-ablations after the 3 months blanking period and before the end of the 9th month after the first procedure are highly recommended.

In the event of aggravating circumstances (new Covid-19 outbreak), these visits can be carried out remotely.

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5.3.7 – Redo procedure

Only one re-ablation procedure is allowed per-protocol between the end of the 3rd month and the end of the 9th month after the first procedure (6-month window).

Re-ablation procedure in Tailored group

In the Tailored group, a re-ablation procedure will be performed using the same approach as the first index procedure. The redo procedure endpoint is also sinus rhythm conversion by ablation at dispersion regions and potential subsequent AT. In addition, a CTI anatomical line is allowed.

If the repeat procedure is performed for an AT recurrence, AF induction is not required at the beginning of the procedure.

Re-ablation procedure in Anatomical group

During a repeat ablation in the Anatomical group, PV reconnections will be checked, and potentially reconnected PV will be re-isolated.

A maximum of two additional anatomical lines are allowed (0, 1 or 2 lines): roof and/or mitral isthmus and/or CTI lines or posterior box isolation (no other lines are allowed).

The redo procedure endpoint is isolation of all four PVs and lines validation.

In case of regularization into AT during anatomical re-ablation, mapping (without VX1) and ablation of the AT is allowed. If the repeat procedure is performed for an AT, it can be mapped (without VX1) and ablated.

5.3.8 – Blanking periods

After the index procedure, a 6-week absolute blanking period will be applied, during which a repeat procedure is not allowed, only cardioversions are allowed if necessary.

After this absolute blanking period and before the end of the standard 3-month blanking period, a repeat procedure is discouraged but not prohibited. The decision to perform a repeat procedure before the end of the 3-month blanking period is left to the operator's discretion. If a repeat procedure is performed during the 3-month blanking period, the recurrence and the repeat procedure are counted as occurring at 3 months.


After a repeat procedure, a 2-week blanking period will be applied, during which AF/AT recurrences will not be counted. Any re-repeat procedures will be performed outside the study according to the operator's preferred approach and will result in the data being censored at the time of the re-repeat procedure. The patient will however stay in the study for safety purposes.

5.3.9 – Visit schedule

Study visits that do not occur within time windows in Table 8 will be considered protocol deviations.

Table 8: Time windows for study visits

Visit	Screening, enrollment, and randomization	Index procedure	3-month follow-up	Redo procedure (if required)	6-month follow-up	12-month follow-up
Timing	Prior to index procedure	0 – 90 days after enrollment	2M + 1 day to 3M after index procedure	3M to 9M after index procedure	6M ± 30 days after index procedure	12M ± 30 days after index procedure


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5.3.10 – Summary of required clinical assessment and data collection

Table 9 summarizes study visits and required assessments and data collection.

Table 9: Schedule of events

Event	Screening	Enrollment	Index procedure	3-month follow-up visit	Redo procedure (if required)	6-month follow-up visit	12-month follow-up visit	Unscheduled follow-up visit
Inclusion and exclusion criteria assessment	X							
Informed consent	X							
Demographics, medical history, cardiac diagnosis		X						
Documentation of AF (ECG, physician's letter)		X						
12-lead ECG		X		X		X	X	X
Physical exam		X		X		X	X	X
Concomitant cardiac medications		X	X	X	X	X	X	X
AF assessment (AF presence and/or AF recurrence since last follow-up)		X	X	X	X	X	X	X
QoL questionnaire		X		X		X	X	
24h ambulatory continuous ECG (Holter)				X		X	X	
Adverse Events review		X	X	X	X	X	X	X
AF interventional procedure			X		X			

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5.4 – Investigators and sites

Investigators selected to participate in this study:

- must be experienced in AF/AT ablation and must have been validated by the coordinating investigator
- must be willing to accept the responsibilities of investigator
- must allow the Sponsor's designated monitors and representatives to review the records pertaining to this study, source documentation and patient informed consents
- must allow eventual internal or external Quality Assurance visit

Each investigator of this study must be trained to the visual detection of dispersion, the use of VX1 and to this protocol. In addition, each investigator must have participated to at least one case by a Volta Medical EP (live or video) and must have performed at least 2 training or roll-in cases in compliance with the Tailored group ablation workflow before inclusions can begin. These patients will not be included in the study and will not be followed-up after ablation.

The presence of a Field Technical Engineer (FTE) from Volta Medical is mandatory for at least the initial cases of the study in order to support investigators.

Considering the possibility of a new Covid-19 outbreak leading to restrictions on travel and access to hospitals, it should be possible for Volta Medical FTEs to support cases remotely, by means of appropriate remote video systems.

Before participating in the study, all investigators must agree to respect and fulfil the terms of this investigational plan and sign and date an Investigator Agreement (cf. Appendix 18.5).

The coordinating investigator of this study is:

Prof. Isabel DEISENHOFER
German Heart Centre Munich
Lazarettstraße 36
80636 Munich, GERMANY

The updateable list of expected investigators and Investigation sites is provided in Appendix 18.7.

During the progress of the Study, according to local regulatory requirements, additional centers and/or other investigators may take part in the Study. In that case, the relevant Ethics Committees, IRBs, and Regulatory Authorities, as well as all investigators, will be notified.

5.5 – Steering Committee

The study is driven by a Steering Committee, whose members are listed in Appendix 18.8. This committee will be actively involved in the investigation and review its progress at regular intervals. At any time, this committee may request that the investigation be put on hold or even terminated for safety, ethical or other reasons.


5.6 – Monitoring plan

The study will be monitored periodically at each enrolling site per the study monitoring plan, for the purpose of:

- Verifying compliance to the protocol (deviations) and applicable regulations (signed informed consent forms),
- Verifying that study documentation exists,
- Verifying case report form data to original entries in source files (discrepancies, missing data).

Volta Medical delegates the responsibility for ensuring proper monitoring of the Study to Labcorp.

The detailed monitoring plan is developed by Labcorp and validated by Volta Medical.

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Appropriate qualified and trained Labcorp employees or representatives will monitor the study according to Labcorp standard operating procedures.

Qualification visits: the monitor will evaluate the investigation sites to ensure that they have the appropriate qualifications and resources and have access to a sufficient number of patients to participate in the Study.

Initiation visits: the monitor will then initiate each Investigation site and will ensure that the Principal Investigator and his team:

- have received and understood the requirements and content of the Clinical Investigation Plan, the Investigator's Brochure, the Informed Consent Form, the eCRF and the Instructions for Use,
- have been trained to the use of the device studied,
- have been informed of their responsibilities.

Monitoring visits: each investigation site will undergo in-site and remote monitoring visits during the Study duration, as defined in the monitoring plan.

Termination visits: closing activities will be carried out by the monitor at each investigation site.

Volta Medical and representatives of regulatory health authorities are permitted to inspect the study documents (protocol, case report forms, study-related medical records, study correspondence, etc.). In addition to ongoing monitoring of the study, GCP audits by the Sponsor or its representatives are also permitted. All attempts will be made to preserve subject confidentiality.

VI – STATISTICAL CONSIDERATIONS


6.1 – Design, statistical methodology and analytical procedures

Standard summary statistics will be calculated for all study variables (demographics and outcomes) by study group and for all patients. For continuous variables, statistics will include means, standard deviation and 95% confidence intervals for means when assumptions of normal distribution are not violated. Median and quartiles may also be presented. Categorical variables will be summarized using frequency distributions.

The analysis for the primary endpoint will be a modified Intention-To-Treat (mITT) analysis, allowing exclusion of some randomized subjects in a justified way:

- Patients that are deemed ineligible after randomization or that do not have any AF ablation will be excluded
- Patients in the Tailored group for whom AF cannot be induced and who undergo conventional ablation will be included in this analysis
- Patients lost to follow-up (death, disability, relocation, or drop-out) during the 3-month blanking period will be excluded
- Patients who complete at least their 3-month follow-up but who are lost to follow-up (death, disability, relocation, or drop-out) before the 12-month follow-up will be included in the analysis and the data will be censored
- Patients who undergo a 3rd ablation procedure (re-repeat procedure) will be included in the analysis but the data will be censored at the time of the 3rd procedure.

A per-protocol (PP) population will also be evaluated and will serve as supportive analyses to the mITT analysis. In the PP analysis, the population will be analyzed according to the treatment actually received at the start of the study, and will consist of patients that met all the inclusion criteria, none of the exclusion criteria, were successfully treated, had no important protocol deviations and attended all the scheduled follow-up visits.

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6.2 – Sample size

The primary endpoint is freedom from AF, 12 months after a single ablation procedure. As observed from previously published studies in patients receiving PVI alone for persistent AF, it could be assumed that at most 62% of the patients in the anatomical group will be free from AF at the end of follow-up^{5,8}. A previous study conducted on VX1 suggested that at least 77% of the patients of the tailored group may be free from AF at the end of follow-up (i.e. Hazard Ratio (HR) 0.547). In order to confirm these results prospectively in this study, 292 patients (146 in each group) are required to show that time to AF is significantly different between groups (Log-Rank test for a one-sided superiority trial, significance level $\alpha=0.025$, statistical power of 80%, under the assumption that the hazard rates are proportional).

Assuming a drop-out rate of 22% (no ablation performed or loss to follow up), **374 patients are required overall** (187 in each group).

Sample size calculations performed using SAS Proc Power TwoSampleSurvival (SAS Institute Inc., Cary, NC)

6.3 – Degree of significance and power of the clinical investigation

Assumptions for the superiority endpoint include a one-sided 0.025 alpha level and 80% power.

6.4 – Expected drop-out rate

We expect a maximum drop-out rate of 22% (i.e. a maximum of 82 patients among the 374 patients are expected to fail to complete the 12-month follow-up).

6.5 – Evaluation criteria for primary and secondary endpoints

6.5.1 – Long-term effectiveness primary endpoint

For the primary endpoint, both Tailored (Treatment) and Anatomical (Control) groups will be compared in a superiority context employing a superiority margin of 15%, as established above in the sample size calculations and as the VX1 has demonstrated in a previous study (HR 0.547).

Formally, the one-sided hypothesis to be tested (Log-Rank test) is:


- H_0 : HR is over 0.547, indicating that the proportion of patients free from AF recurrences at 3-12 month in the Treatment group is not superior to the proportion of patients free from AF recurrences at 3-12-month in the Control group plus 15% margin.
 H_0 : $HR > 0.547$
- H_1 : HR equals or is less than 0.547, indicating that the proportion of patients free from AF recurrences at 3-12 month in the Treatment group is superior to the proportion of patients free from AF recurrences at 3-12-month in the Control group plus 15% margin.
 H_1 : $HR \leq 0.547$

The null hypothesis will be rejected if the p-value is less than the significance level of 0.025.

If the Treatment group is found to have a statistically significantly greater freedom from AF rate than Control, the Treatment will be considered superior relative to Control.

In addition, the time to AF recurrence in each group will be visually compared by Kaplan-Meier curves.

The impact of any baseline demographic factor, which is found to be significantly different between the treatments, will be assessed.

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6.5.2 – Other secondary and exploratory endpoints

For all other survival data, one-sided and two-sided Log-Rank test will be applied at a significance level of 0.05 (secondary/exploratory endpoints 2-9). The secondary efficacy endpoints will be evaluated in a pre-specified order following a gatekeeping approach so that subsequent endpoints will be evaluated if and only if the previous endpoint was found to achieve statistical significance. Thus, no correction for multiple testing will be required. Further details including the ordering of endpoints will be provided in the statistical analysis plan (SAP).

For quality of life (endpoint 10), a linear mixed model for repeated data will be used to examine the difference between groups over time.

For all other endpoints:

The continuous variables will each be analyzed by a Student's t-test, and equivalent non-parametric method, the Wilcoxon–Mann–Whitney test, will be used in case of violation of the normality assumption. Chi-square test or Fisher exact test will be used for the categorical data.

6.6 – Interim analysis

This trial will employ an adaptive design for the blinded re-estimation of the sample size. To ensure the study is adequately powered for the superiority comparison for the primary outcome measure, the assumptions regarding the rates of AF in both study arms will be verified after 50% of the originally planned total patient sample have complete primary endpoint information. A conditional power approach for sample-size re-estimation using the Mehta-Pocock²⁵ approach will be utilized. Following this interim assessment, the sample size may only remain the same or be increased. Details of the statistical calculations to be utilized in support of the interim analysis will be provided in the study Statistical Analysis Plan (SAP). The SAP will also provide details regarding the operational procedures for conducting, reporting, and acting on the results of the analysis.

A third-party, independent statistician will perform this analysis to minimize operational bias. After the analysis, the statistician will provide a recommendation to the Steering Committee and Volta Medical. The recommendation will also be shared with senior, non-operational management staff that have a strict business need to review and act on the results. None of the clinical operational staff or study investigators will have access to the interim data on which the analysis is based in order to further minimize operational bias. The scientific soundness of the study is not likely to be impacted as the only potential change to the study as a result of this analysis is an increase in sample size.

6.7 – Missing data and sensitivity analysis

Subjects who miss a study visit should be contacted immediately by the Investigational site to determine the reason for the missed visit and to reschedule the visit as soon as possible to meet the study visit window. If the subject cannot be located after 3 attempts by phone, email and/or letter, then the subject will be considered lost to follow-up. All attempts to contact the subjects will be documented and retained in the subject study record.


With regard to the main judgement criteria, data will be censored if the patient is lost to follow-up (death, disability, relocation, or drop-out).

As the burden of study participation does not differ between the tailored and the anatomical arm, we expect all study losses to be non-differential with respect to treatment assignment. Thus, our results will not be biased as a result of these losses.

Additional supportive analyses will be performed on the primary endpoint to assess the effect of missing data.

For missing demographic data, the data will not be replaced because it has no weight on the main judgment criterion.

A rigorous monitoring is expected, any missing data will be filled in during these visits.

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6.8 – Minimum and maximum number of subjects to be included for each site

A maximum of 75 inclusions per site (20% of inclusions) will be allowed in order to prevent site-effect. This limit will ensure a minimum of 5 enrolling sites.

6.9 – Poolability of Sites

All investigational sites will follow the requirements of standardized data collection procedures and forms. The primary efficacy and safety endpoints will be presented separately for each site using descriptive statistics. Poolability of the primary efficacy endpoint across investigational sites will be evaluated using a logistic regression model with a fixed effect for site. If there is a significant effect of site, analysis will be repeated using site as a random effect. Sites enrolling fewer than 5 subjects will be combined to form one quasi site. Additional exploratory analyses may be performed to understand any variations in outcome by site. Assessment of poolability by geography (US vs. OUS) will be performed based on logistic regression as described above. As US subjects will only be patients with AF duration of 3 months to < 12 months, only OUS patients with AF <12 months will be included in the poolability by country assessment. As only one catheter type is approved for use in the US, an additional subgroup analysis of each catheter used will assess the variability, if any, by country for patients with the same catheter type.

VII – RISKS DESCRIPTION AND MINIMIZATION

7.1 – Expected clinical benefits

VX1 offers a fast and reliable way to identify patient-specific spatio-temporal dispersion EGMs. Previous research done by Volta suggests that consistently targeting dispersed EGMs has resulted in less recurrence of AF. In addition, research by Volta Medical has shown that targeting of dispersed electrograms identified by VX1 results in lesser surface area ablated than targeting complex fractionated atrial electrograms (CFAEs). In targeting these dispersed electrograms in addition to conventional approaches, patients may benefit from fewer redo AF ablation procedures and less recurrence of atrial arrhythmias.


7.2 – Expected adverse effects of the device

The use of VX1 is not expected to increase the likelihood of any adverse effect that might otherwise occur during a cardiac ablation. Use of the VX1 device has been characterized by longer mapping time than observed in comparable patient populations in literature, however procedure times and ablation time have not shown to be longer. Complications associated with AF ablation procedures are well-documented and anticipated. Risks for cardiac ablation include, but are not limited to those identified in section 14.3 – Anticipated adverse events.

7.3 – Risks associated with participation in the clinical investigation

Subjects randomized into the Tailored arm of the study are expected to receive higher RF times, greater ablation area, and slightly longer procedure times than subjects randomized to the anatomical arm. However, previous research indicates that RF time, ablation area, and procedure time while using the VX1 system are well within accepted industry standards for AF ablation and consistent with other approaches to AF ablation in published literature. The study design assumes that all patients receive the standard of care and expect additional benefits linked to close and repeated follow-ups after AF ablation.

The procedures and methods for data collection required by the protocol do not differ from routine AF ablation and post-ablation follow-up practice, other than filling out a Quality-of-Life questionnaire at baseline and at each follow-up visit.

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Use of the device not in conformance with this investigational plan and/or with the instructions in the physician's manual could introduce other issues.

7.4 – Measures to control or mitigate risks

To protect the welfare of subjects, Ethics Committee or IRB approval of the investigation will be obtained for each site prior to the first case at that site.

Investigators selected to participate in this study will have experience in AF ablation. Trained and experienced clinical and technical personnel representing Volta Medical will be made available to support procedures and for troubleshooting.

All areas recommended for ablation by the VX1 system will be reviewed by the investigator, and if the investigator determines that the recommended region is undesirable for ablation the investigators will be instructed to maintain the subject's safety first and avoid ablation of undesirable regions. The frequency of such divergent assessments will be documented and evaluated.

Each investigator will sign an Investigator Agreement stating his/her responsibility to conduct this study according to this investigational plan, to adhere to the records and reporting requirements, and to supervise use of the device.

Through careful design and testing, Volta Medical has attempted to minimize the risk to patients. Testing included: software validation testing, electrical safety and electromagnetic compatibility testing according to IEC 60601 standards on the hardware system.

VX1 Application has received CE mark on 14 JAN 2020, VX1 Hardware has received CE mark on 09 JUL 2020.

Copy of the CE certificates are in Appendix 18.3.

Volta Medical Quality Management System is ISO 13485 certified.

7.5 – Justification of the risk-benefit ratio

Considering the potential risks, the measures taken to minimize risks and the potential benefit to patients, the risk-benefit ratio is deemed acceptable for the use of VX1 and for the conduct of this study.


VIII – DATA MANAGEMENT

Electronic Data Capture (EDC) will be used for this investigation for collecting the data. The EDC/eCRF system will be managed by Labcorp according to Labcorp standards. Confidentiality of patient identity will be ensured.

A complete detailed guideline on data to be recorded for the study and how to fill in the eCRFs will be provided to the Investigators.

Data will be reviewed and cleaned, as well as data queries issued and resolved, in accordance with the Data Management Plan.

Audits or inspections by Competent Authorities and FDA may be carried out.

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IX – AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

Major changes to the protocol will be described in a Clinical Investigation Plan Amendment. The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

The principal investigator will acknowledge the receipt of the amendment and confirm by their signature on the Amendment Signature page that they will adhere to the amendment.

The amendment must be submitted to the relevant Ethics Committees or IRB and to Authorities, where required. Approval from the Ethics Committees or IRB will be required prior to implementation of the amendment.

Any amendment affecting the patient requires that the patient be informed of the changes and a new consent be signed and dated by the investigator and patient prior to the patient's next follow-up.

Changes to, or formal clarifications of, the clinical investigational plan will be documented in writing and provided to investigators. This information will be incorporated when an amendment occurs.

X – DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

10.1 – General


A protocol deviation is defined as any event where the clinical investigator or site personnel did not conduct the study according to the protocol.

The Investigator is not allowed to deviate from the Clinical Investigation Plan.

In emergency situations, deviations from the Clinical Investigation Plan, established in order to protect the rights, safety and well-being of the subjects, may be carried out without authorization of Volta Medical or Ethics Committee/IRB prior approval. Such deviations should be recorded and forwarded as soon as possible to Volta Medical and the appropriate Ethics Committee or IRB.

In particular, every effort should be made to avoid deviations from the protocol including, but not limited, to the following:

1. Inclusion of a patient without appropriate written consent or who does not meet the inclusion criteria or who meets any of the exclusion criteria,
2. Missing any data related to the primary and secondary endpoints,
3. Use of other energy than RF for ablation (cryo/chemical),
4. Ablation other than antral PVI in the Anatomical arm for index procedures (e.g. lines other than ICT, EGM ablation, PV encirclement other than antral),
5. Ablation other than PVI \pm lines (as defined in 5.3.7 – Redo procedure) in the Anatomical arm for redo procedures,
6. Failure to terminate AF with incomplete mapping in the Tailored group (mono atrial mapping, too short mapping < 20 minutes),
7. Failure to terminate AF with incomplete ablation in the Tailored group, leaving dispersion areas not ablated, without valid justification (for safety reasons at operator's discretion),
8. Failure to terminate AF without a mandatory second mapping/ablation cycle in the Tailored group,
9. Patient becoming unblinded to his/her randomization assignment,
10. Follow-up being performed outside the time window allowed.

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10.2 – Procedures for recording, reporting and analyzing deviations from the Clinical Investigation Plan

Protocol deviations shall be reported to the Sponsor regardless of whether medically justifiable or taken to protect the patient in an emergency.

Subject-specific deviations will be reported on the Labcorp Risk and Issues Management System (RIMS).

Non-subject specific deviations (e.g. unauthorized use of a study device by a physician who has not signed an investigator agreement, etc.) will also need to be reported to the Sponsor.

Investigators will also adhere to procedures for reporting study deviations to their Ethics Committee or IRB in accordance with their specific reporting policies and procedures.

For reporting purposes, the Sponsor classifies study deviations as important or non-important. Important deviations are defined as changes in the conduct of the trial from that specified in the protocol that compromise the subject's rights, safety, or well-being, or the completeness, accuracy, reliability or scientific integrity of the study data. The following deviations are considered to be important:


1. Enrollment of a patient without written consent
2. Failure to report SAEs
3. Crossovers between the groups
4. Use of other energy than RF for ablation (cryo/chemical)
5. Ablation other than antral PVI in the Anatomical arm for index procedures (e.g. lines other than ICT, EGM ablation, PV encirclement other than antral),
6. Ablation other than PVI \pm lines (as defined in 5.3.7 – Redo procedure) in the Anatomical arm for redo procedures,
7. Failure to terminate AF with incomplete mapping in the Tailored group (mono atrial mapping, too short mapping < 20 minutes),
8. Failure to terminate AF with incomplete ablation in the Tailored group, leaving dispersion areas not ablated, without valid justification (for safety reasons at operator's discretion),
9. Failure to terminate AF without a mandatory second mapping/ablation cycle in the Tailored group,

Deviations not classified as important will be considered non-important. Protocol deviations will be classified by the Steering Committee in a blinded fashion. Patients presenting with at least one important deviation will be excluded from the Per-Protocol (PP) analysis.

10.3 – Corrective and preventive actions and criteria for disqualification of the Principal Investigator

In the event of 2 important deviations at the same investigation site, an assessment will be made by the Sponsor and the site principal Investigator may be disqualified. In that case, the inclusions will be stopped at that site.

XI – DEVICE ACCOUNTABILITY

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The Principal Investigator of each site shall maintain adequate records of the receipt and disposition of all devices per local institutional procedures and regulations.

XII – STATEMENTS OF COMPLIANCE

12.1 – Ethical and regulatory considerations

The study will be conducted in accordance with the ethical principles mentioned in the Declaration of Helsinki (cf. Appendix 18.1), Good Clinical Practice, the ISO 14155 Standard and applicable laws and country regulations where the study will be performed.

This study would not start until approvals or favorable opinions have been received from applicable Ethics Committees or IRBs and Regulatory Authorities.

Each amendment to this Clinical Investigation Plan must be approved beforehand by the applicable Ethics Committees or IRBs and Regulatory Authorities for the full duration of the Study.

Any requirements imposed by the applicable Ethics Committees, IRBs and/or Regulatory Authorities shall be respected and applied throughout the Study period.

12.2 – Insurance

Provided that this protocol is respected, the civil liability of Volta Medical and all its agents is covered by a contract subscribed by Volta Medical with HDI GLOBAL SE (contracts nos. 0100534514058-200083 for France, 390-76236600-30016 for Belgium, 76237332-03032 for Germany and V-071-369-378-0 for The Netherlands). A copy of the insurance certificates can be found in Appendix 18.2.

XIII – INFORMED CONSENT PROCESS

To participate in the study, the subject must sign and date the Informed Consent Form after having been informed about the nature and purpose of the Study, participation and termination conditions, risks, and benefits, before initiation of any study-related procedures. Patient Information and Patient Informed Consent Form are provided in Appendix 18.4.

A copy of the signed Informed consent Form must be provided to the participating patient.


The patient information and Informed Consent Form will be available in certified translation in all official languages of the countries participating in the Study.

Signed Informed Consent Forms must remain in the patients' study files and be available for verification by the Sponsor or representative at any time.

XIV – ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

14.1 – Definitions (according to ISO 14155:2020)

Adverse Event (AE)

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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 investigational medical device and whether anticipated or unanticipated.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

NOTE 3: This includes 'comparator' if the comparator is a medical device.

Serious Adverse Event (SAE)

Adverse event that led to any of the following:

- a) death,
- b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
 - a life-threatening illness or injury, or
 - a permanent impairment of a body structure or a body function including chronic diseases, or
 - in-patient or prolonged hospitalization, or
 - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function.
- c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, 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 risk assessment.

NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.


Device deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

NOTE 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

NOTE 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

Device malfunction

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Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB.

Use error

User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user.

NOTE 1: Use error includes the inability of the user to complete a task.

NOTE 2: Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment.

NOTE 3: Users might be aware or unaware that a use error has occurred.

NOTE 4: An unexpected physiological response of the patient is not by itself considered a use error.

NOTE 5: A malfunction of a medical device that causes an unexpected result is not considered a use error.

14.2 – Adverse event evaluation and reporting

Conditions or diseases which are pre-existing and chronic should not be recorded as adverse events. Changes in a chronic condition or disease that are consistent with natural disease progression are not considered adverse events. Pre-existing conditions or diseases should be documented as part of the patient's medical history.

Elective or pre-planned treatments for AF (e.g. scheduled re-ablation or cardioversion) which are part of the patient's scheduled treatment plan should not be considered adverse events. However, any events related to a procedure (including re-do procedure) or the patient's underlying AF which are not expected or indicate a worsening of condition should be reported as adverse events.

The adverse event should be recorded in standard medical terminology rather than the patient's own words when possible.

The investigator will assess each adverse event for its relationship to the study device, and whether it was anticipated in the protocol. The determination of the relationship between the adverse event and the device or procedure is made according to the following definitions:


- Definitely related (causal relationship): the adverse event was directly and clearly related to the device or procedure
- Probably related
- Possibly related
- Not related
- Unknown

Adverse events that are serious and/or unanticipated will be reviewed immediately by Labcorp and Volta employees or representatives and will also be reviewed during DSMB meetings.

All adverse events are listed in the eCRF.

All serious adverse events (SAEs, SADEs, USADEs) should be emailed to SAEIntake@labcorp.com within 24 hours from the become aware date. The following information should be collected:

- Nature of adverse event
- Date of onset of adverse event
- Date of resolution of adverse event, if applicable
- Statement as to why it is considered serious
- Statement as to why it is considered unanticipated, if applicable
- Statement as to the degree to which it is considered device related, and why

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- Results of any diagnostic tests performed
- Description of any intervention performed, or treatment administered

It is the responsibility of each investigator to report all SAEs/SADEs/USADEs to the Ethics Committee or IRB, according to national regulations and EC/IRB requirements.

Volta Medical will assure that Labcorp employee or representative will report all serious adverse events to the corresponding Competent Authorities in accordance with all applicable national regulations.

14.3 – Anticipated adverse events

Table 10 provides the list of all anticipated adverse events related to AF ablation.


Table 10: Anticipated Adverse Events

Description	Description
Abnormal ECG	Pericardial effusion
Local normal discomfort due to insertion/removal of vascular sheaths	Cardiac tamponade due to perforation
Hemorrhage and/or hematoma at sheath insertion	Nerve injury
Extremity weakness, swelling and/or pain	Air embolism
Complete AV block	Allergic reaction
Nausea/vomiting	Endocarditis
Shortness of breath/dyspnea	Esophageal-atria fistula
Feeling of chest pain, skipped beats, and/or rapid heart rate	Hemothorax
Damage to skin from prolonged exposure to x-rays	Pericarditis
New arrhythmias	Pseudoaneurysm
Ventricular arrhythmia requiring defibrillation	Pulmonary vein dissection/stenosis
Arterial injury requiring intervention	Respiratory failure
Thromboembolism	Stroke/TIA
Local/systemic infection	Valvular damage
Pneumothorax	Pleural effusion
AV fistula	Pulmonary edema
Thrombophlebitis	Anemia requiring transfusion
Pulmonary embolism	Vasovagal reaction
Myocardial infarction	Hypotension
Heart failure	Death (must be reported as SAE)

14.4 – Data Safety Monitoring Board (DSMB)

A board of independent experts will review the study data to determine the progress of the study from a safety point of view and will independently make recommendations to the Steering Committee to continue, to modify or to terminate the clinical study.

The DSMB will consider relevant background knowledge about the disease, therapies, or patient population as well as study-specific data, in order to monitor the conduct of the study to evaluate the safety of the subjects involved in the trial, to evaluate the occurrence of early unanticipated adverse effects.

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In particular, the board will review all the Adverse Events in order to ascertain evidence of a safety risk in continuing the study.

The DSMB is made of three independent EP experts (cf. Appendix 18.8).

XV – SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

15.1 – Criteria and provisions

Premature, definitive, or temporary termination of all or part of the study may be decided by Ethics Committees, IRBs, Competent Authorities or the Sponsor.

If an adverse effect due to the implementation of the protocol is observed, the study may be suspended at any time by the Sponsor. If no satisfactory solution can be found to the problem, the study may be stopped completely; if a satisfactory solution is found, the study may be resumed.

Premature termination of the study may occur motivated by a general decision (Ethics Committees, IRBs, regulatory Competent Authorities, Data Safety Monitoring Board) for safety reasons related to the use of the device or study procedures.

A site may be terminated for the following reasons: failure to comply with the conditions of the study protocol and/or failure to accurately complete case report forms.


15.2 – Patient follow-up requirements

At the end of the study, medical management of patients will consist of standard post-ablation follow-up, regardless of whether the study has ended normally or prematurely.

XVI – STUDY REPORT AND PUBLICATION POLICY


After conclusion of the investigation, a comprehensive clinical and statistical report shall be written by Volta Medical in consultation with the Coordinating Investigator.

The first publication will be a full publication of all data from all sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by investigators or their representatives will require pre-submission review by Volta Medical. Volta Medical is entitled to delay publication in order to obtain patent protection. For more details regarding publications, refer to the publication Agreement.


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XVII – BIBLIOGRAPHY


1. Kirchhof, P. *et al.* A roadmap to improve the quality of atrial fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm Association consensus conference. *Europace* **18**, 37–50 (2016).
2. Morin, D. P. *et al.* The State of the Art: Atrial Fibrillation Epidemiology, Prevention, and Treatment. *Mayo Clin. Proc.* **91**, 1778–1810 (2016).
3. Rahman, F., Kwan, G. F. & Benjamin, E. J. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* **11**, 639–654 (2014).
4. Sheikh, A. *et al.* Trends in hospitalization for atrial fibrillation: epidemiology, cost, and implications for the future. *Prog Cardiovasc Dis* **58**, 105–116 (2015).
5. Verma, A. *et al.* Approaches to Catheter Ablation for Persistent Atrial Fibrillation. *N. Engl. J. Med.* **372**, 1812–1822 (2015).
6. Oral, H. *et al.* A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. *J. Am. Coll. Cardiol.* **53**, 782–789 (2009).
7. Fassini, G. *et al.* Left mitral isthmus ablation associated with PV Isolation: long-term results of a prospective randomized study. *J. Cardiovasc. Electrophysiol.* **16**, 1150–1156 (2005).
8. Fink, T. *et al.* Stand-Alone Pulmonary Vein Isolation Versus Pulmonary Vein Isolation With Additional Substrate Modification as Index Ablation Procedures in Patients With Persistent and Long-Standing Persistent Atrial Fibrillation: The Randomized Alster-Lost-AF Trial (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation). *Circ Arrhythm Electrophysiol* **10**, (2017).
9. Gaita, F. *et al.* Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* **1**, 269–275 (2008).
10. Elayi, C. S. *et al.* Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. *Heart Rhythm* **5**, 1658–1664 (2008).
11. Vogler, J. *et al.* Pulmonary Vein Isolation Versus Defragmentation: The CHASE-AF Clinical Trial. *J. Am. Coll. Cardiol.* **66**, 2743–2752 (2015).

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12. Haïssaguerre, M. *et al.* Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N. Engl. J. Med.* **339**, 659–666 (1998).
13. Pappone, C. *et al.* Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. *J. Am. Coll. Cardiol.* **42**, 185–197 (2003).
14. Kanj, M., Wazni, O. & Natale, A. Pulmonary vein antrum isolation. *Heart Rhythm* **4**, S73-79 (2007).
15. Atienza, F. *et al.* Real-time dominant frequency mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. *Heart Rhythm* **6**, 33–40 (2009).
16. Atienza, F. *et al.* Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial fibrillation: a noninferiority randomized multicenter RADAR-AF trial. *J. Am. Coll. Cardiol.* **64**, 2455–2467 (2014).
17. Jadidi, A. S. *et al.* Inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation: combined magnetic resonance imaging and high-density mapping. *J. Am. Coll. Cardiol.* **62**, 802–812 (2013).
18. Jadidi, A. S. *et al.* Ablation of Persistent Atrial Fibrillation Targeting Low-Voltage Areas With Selective Activation Characteristics. *Circ Arrhythm Electrophysiol* **9**, (2016).
19. Narayan, S. M. *et al.* Classifying fractionated electrograms in human atrial fibrillation using monophasic action potentials and activation mapping: evidence for localized drivers, rate acceleration, and nonlocal signal etiologies. *Heart Rhythm* **8**, 244–253 (2011).
20. Nademanee, K. *et al.* A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J. Am. Coll. Cardiol.* **43**, 2044–2053 (2004).
21. Seitz, J. *et al.* AF Ablation Guided by Spatiotemporal Electrogram Dispersion Without Pulmonary Vein Isolation: A Wholly Patient-Tailored Approach. *J. Am. Coll. Cardiol.* **69**, 303–321 (2017).
22. Seitz, J. *et al.* Automated Detection of Complex Fractionated Atrial Electrograms In Substrate-Based Atrial Fibrillation Ablation: Better Discrimination with a New Setting of CARTO® Algorithm. *J Atr Fibrillation* **6**, 673 (2013).

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23. Monir, G. & Pollak, S. J. Consistency of the CFAE phenomena using custom software for automated detection of complex fractionated atrial electrograms (CFAEs) in the left atrium during atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **19**, 915–919 (2008).
24. Seitz, J. *et al.* Artificial Intelligence Software Standardizes Electrogram-based Ablation Outcome for Persistent Atrial Fibrillation. *J. Cardiovasc. Electrophysiol.* In press (2022).
25. Mehta, C. R. & Pocock, S. J. Adaptive increase in sample size when interim results are promising: A practical guide with examples. *Statistics in Medicine* **30**, 3267–3284 (2011).

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XVIII – APPENDICES

18.1 – Declaration of Helsinki

18.2 – Insurance Certificate

18.3 – CE Certificates

18.4 – Patient Information and Patient Informed Consent

18.5 – Investigator Agreement

18.6 – IFU or Investigator's Brochure

18.7 – List of Investigators

18.8 – Study Boards