Focal Impulse and Rotor Modulation Ablation versus Pulmonary Vein isolation for the Treatment of Paroxysmal Atrial Fibrillation (FIRMAP AF)

Statistical Analysis Plan (SAP)

PROTOCOL ID:	FIRMAP AF
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1 INTRODUCTION

1.1 Study Overview

1.1.1 Title

FIRMAP AF is a prospective randomized study to assess the safety and effectiveness of FIRM-guided ablation versus conventional pulmonary vein isolation (PVI) ablation for the treatment of paroxysmal atrial fibrillation (AF) for subjects without prior AF catheter ablation.

1.1.2 Objectives

The primary objective is to compare the safety and effectiveness of FIRM-guided ablation procedures with conventional ablation for the treatment of paroxysmal atrial fibrillation (AF) for subjects without prior AF catheter ablation.

The secondary objective is to evaluate the treatment time and quality of life outcomes.

1.1.3 Patient Population

FIRMAP AF will include subjects experiencing at least two (2) documented episodes of paroxysmal atrial fibrillation during the three (3) months preceding study entry with clinical indication for AF ablation per guidelines. At least one episode should be documented by rhythm strip or ECG.
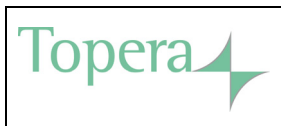
1.1.4 Inclusion Criteria

- Male or female 18 – 80 years of age.
- Experiencing at least two (2) documented episodes of **paroxysmal** atrial fibrillation in the last 3 months preceding study entry with clinical indication for AF ablation per guidelines. At least one episode should be documented by rhythm strip or ECG.
- Indicated for AF ablation according to current EHRA guidelines.
- Prescribed with oral anticoagulation therapy, in indicated patients per the latest EHRA guidelines.
- Willingness and able to remain on anti-coagulation therapy as per the latest EHRA guidelines.
- Left atrial diameter < 5.5 cm as measured and image ((CT/TEE/TTE/ MRI or ICE) documented within previous six months up to pre-procedure.
- Sustained AF (>5 min uninterrupted) during the electrophysiology procedure. If the subject is not experiencing spontaneous, sustained AF, it may be induced by burst pacing (typically from the coronary sinus) with or without isoproterenol infusion in conventional clinical fashion.
- Willingness, ability and commitment to participate in baseline and follow-up evaluations.
- Signed patient informed consent form.

1.1.5 Exclusion Criteria

- Presence of structural heart disease of clinical significance including:
  - Coronary artery disease with either:
    - Coronary artery bypass surgery (CABG) within the last 180 days (six months), or
    - Stable/unstable angina or ongoing myocardial ischemia.
  - Congenital heart disease where either the underlying abnormality or its correction prohibits or increases the risk of ablation.
- NYHA Class III – IV.
- Ejection fraction < 40% (within previous six months).
- History of myocardial infarction (MI) within the past three months.
- Any concomitant arrhythmia or therapy that could interfere with the interpretation of the results from this study.
- ASD closure device, LAA closure device, prosthetic mitral or tricuspid valve, or permanent pacemaker.
- Any previous AF catheter ablation.
- History of prior cardioversion for AF lasting > 48 hours.
- Continuous AF episode lasting > 7 days immediately prior to the procedure without a sinus rhythm.
- Severe electrolyte abnormalities at time of the ablation procedure or atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible non-cardiac cause.
- Atrial fibrillation from a reversible cause (e.g., surgery, hyperthyroidism, pericarditis).
- Contraindication to Heparin and Warfarin/other novel oral anticoagulants (e.g. dabigatran, rivaroxaban, apixaban).
- History of pulmonary embolus within one year of enrollment.
- Acute pulmonary edema.
- Atrial clot/thrombus on imaging such as on a trans-esophageal echocardiogram (TEE) performed within 72 hours of the procedure if deemed appropriate by investigator.
- History of a cerebrovascular disease (including stroke or TIA) within the last 12 months.
- Any anticipation of cardiac transplantation or other cardiac surgery within the next 12 months.
- History of thromboembolic event within the past 3 months.
- Diagnosed atrial myxoma.
- Significant pulmonary disease, (e.g. restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces severe chronic symptoms and significantly increases risk to sedation or anesthesia.
- Acute illness or active systemic infection or sepsis.
- History of blood clotting abnormalities or bleeding abnormalities.
- Life expectancy of less than 12 months.
- Presence of intramural thrombus, tumor, or other abnormality that precludes catheter introduction or safe manipulation.

- Women who are pregnant.

1.1.6 Study Masking

FIRMAP AF is a multi-center, open-label, randomized study (no masking).

1.1.7 Randomization

Block randomization stratified by center will be used to assign subjects (1:1) to the conventional AF ablation treatment with PVI (PVI group), or to the FIRM-guided AF ablation procedure without PVI (FIRM group).

1.2 Study Outcomes

1.2.1 Primary Outcomes

1.2.1.1 Acute Safety

Freedom from procedure-related serious adverse events within 7 days of the procedure.

1.2.1.2 Long Term Safety

Freedom from procedure-related serious adverse events within one year of the index procedure.

1.2.1.3 Acute Effectiveness (secondary endpoint only)

FIRM group: Elimination of identified AF rotors

Control group: Isolation of all pulmonary veins

1.2.1.4 Long Term Effectiveness (primary effectiveness endpoints)

Single-procedure freedom from AF recurrence from 3-12 months after the index AF ablation procedure (with 90-day blanking period).

*Freedom from AF recurrence is defined as no documented episodes of AF > 30 seconds with conventional non-invasive monitoring. In the case of a cardiac implanted electronic device (CIED), freedom from AF recurrence is defined as no documented episodes of AF > 30 seconds in a 72-hour window at the follow-up visits in addition to any symptomatic episodes with documented AF > 30 seconds.

1.2.1.5 Secondary Outcomes

1.2.1.5.1 Acute Effectiveness

AF termination or CL prolongation:

1.   Termination of spontaneous or induced AF by ablation of the source of arrhythmia

2. Reduction of the mean AF rate (total time measured across 10 consecutive cycles in the coronary sinus divided by 10) by least 10% by ablation of the source of arrhythmia

1.2.1.5.2 Long-Term Effectiveness

1. Single-procedure freedom from AF/AT recurrence from 3-12 months post index ablation procedure (with 90-day blanking period).

2. Freedom from symptomatic AF/AT recurrence from 3-12 months post index ablation procedure (with 90-day blanking period).

3. Freedom from AF recurrence from 0-12 months post index ablation procedure (without 90-day blanking period).

4. Freedom from AF recurrence at 12 months post index ablation procedure (can include repeat procedures).

1.2.1.5.3 Quality of Life

Impact on quality of life, using patient-reported outcome instruments (EQ-5D and AFEQT), within treatment groups (change from pre-procedure to post-procedure follow-up timepoints) and between treatment groups. Analysis will be performed if primary endpoints are met.

1.2.1.6 Additional Evaluations

1.2.1.6.1 Total RF Ablation Time

Total RF ablation time as measured by total time of ablation lesion applications, from first ablation lesion to end of last lesion, will be documented. These values will be compared between the FIRM-guided and conventional ablation groups.

If ablation for AT/atrial flutter is pursued, this ablation time will be documented separately

1.2.1.6.2 Total Radiation Exposure

As above, these values will be compared between the FIRM-guided and PVI groups.

1.2.1.6.3 Repeat procedure and hospitalization

Any information regarding repeat procedures and re-hospitalizations will be collected and compared between groups

1.2.1.6.4 Economic Analysis

Cost-effectiveness analysis based on clinical and patient-reported outcomes and resource utilization. Analysis will be performed if primary endpoints are met.

2 Statistical Methods

2.1 General Analysis Principles

All primary endpoint analyses will be conducted under the principle of "Intention-To-Treat" (ITT), where each subject randomized to a treatment group who has had a mapping and/or ablation catheter inserted shall be considered part of the ITT group. As a secondary exploratory analysis, a "Per Protocol" (PP) analysis may be performed with a subgroup of the ITT group who have no major protocol deviations reported.

2.2 Study Endpoints

2.2.1 Long-Term Effectiveness (Primary effectiveness endpoint)

The primary effectiveness endpoint is single-procedure freedom from AF/AT recurrence from 3-12 months after the index AF ablation procedure (with 90-day blanking period)..

The hypothesis to be tested is the recurrence rate for FIRM-guided AF ablation is not inferior to that experienced by the conventional AF ablation arm.

The statistical hypothesis for this endpoint is operationalized as follows:

H_0: δ > .15

H_A: δ < .15

α = .05 (two-tailed)

Where:

$\delta = p_C - p_F$

p_C = Proportion free from AF recurrence at twelve (12) months post index ablation procedure for the conventional AF ablation arm (.50)

p_F = Proportion free from AF recurrence at twelve (12) months post index ablation procedure for the FIRM-guided AF ablation arm (.55)

The non-inferiority margin for this hypothesis is 15% (.15). If the lower limit of the two-sided 95% confidence interval calculated for the difference in proportions (δ) is less than .15, the null hypothesis will be rejected and evidence in favor of the alternative (FIRM-guided ablation for atrial fibrillation is not inferior to conventional ablation for atrial fibrillation) affirmed.

This non-inferiority margin was chosen based on that used in the FreezeAF[1] and VGLB[2] trials.

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[1] Luik, Armin MD, et. al. (2010). Rationale and design of the FreezeAF trial: A randomized controlled noninferiority trial comparing isolation of the pulmonary veins with the cryoballoon catheter versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation. American Heart Journal. 159(4):555-560.

The proportion of successes in each treatment arm shall be estimated using Kaplan-Meier survival estimation.

2.2.2 Acute Effectiveness (Secondary effectiveness endpoint)

The acute success of each arm shall be determined by:

1. A subject in the FIRM-guided ablation arm shall be classified as an acute success upon elimination of all identified atrial fibrillation rotors.
2. A subject in the conventional ablation arm shall be classified as an acute success upon isolation of all pulmonary veins.

The proportion of successes in each arm will be calculated as follows:

$$\frac{n}{N}$$

Where:

n = the total count of "successful" subjects in the arm in question

N = the total count of subjects for that arm in the ITT group

The statistical hypothesis for this endpoint is operationalized as follows:

H_0: $p_F = p_C$

H_A: $p_F \neq p_C$

$\alpha = .05$ (two-tailed)

Where:

p_F = the proportion of "successes" in the FIRM-guided ablation arm

p_C = the proportion of "successes" in the conventional ablation control arm

The analysis to be performed for this endpoint will be a Chi-square test of Independence.

2.2.3 Acute Safety

The acute safety success of either treatment arm is defined as freedom from serious adverse events related to the procedure within seven (7) days of the index procedure.

The proportion of successes in each arm will be calculated as follows:

$$\frac{n}{N}$$

Where:

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[2] Dukkipati,, Srinivas R. MD, et. al. (2015). Pulmonary Vein Isolation Using the Visually Guided Laser Balloon. Journal of the American College of Cardiology. 66(12):1350-1360.

n = the total count of subjects presenting freedom from serious adverse events related to the procedure within seven (7) days of the index procedure.

N = the total count of subjects in that arm in the ITT group

The statistical hypothesis for this endpoint is operationalized as follows:

H_0: $p_F = p_C$

H_A: $p_F \neq p_C$

α = .05 (two-tailed)

Where:

P_F = the proportion of "successes" in the FIRM-guided ablation arm

p_C = the proportion of "successes" in the conventional ablation control arm

The analysis to be performed for this endpoint will be a Chi-square test of Independence.

2.2.4 Long-Term Safety

Long-term safety is defined as freedom from serious adverse events related to the procedure (including those related to repeat procedures) within one year of the index procedure.

The statistical hypothesis for this endpoint is operationalized as follows:

H_0: $p_F = p_C$

H_A: $p_F \neq p_C$

α = .05 (two-tailed)

Where:

P_F = the proportion of subjects free from serious adverse events related to the procedure (including those related to repeat procedures) within one year of the index procedure in the FIRM-guided ablation arm

p_C = the proportion of subjects free from serious adverse events related to the procedure (including those related to repeat procedures) within one year of the index procedure in the conventional ablation control arm

The proportion of successes in each treatment arm shall be estimated using Kaplan-Meier survival estimation.

2.3 Additional Secondary Investigations

Secondary Endpoints (unpowered) include:

1. AF termination or CL prolongation, as identified by:

a. Termination of spontaneous or induced AF by ablation of the source of arrhythmia.

b. Reduction of the mean AF rate by at least 10% by ablation of the source of arrhythmia.

2. Single-procedure freedom from AF recurrence from 3-12 months post index ablation procedure (with 90-day blanking period) (Long-Term Effectiveness).

3. Freedom from symptomatic AF/AT recurrence from 3-12 months post index ablation procedure (with 90-day blanking period).

4. Freedom from AF recurrence from 0 – 12 months post index ablation procedure (without 90-day blanking period) (Long-Term Effectiveness).

5. Freedom from AF recurrence at 12 months post index ablation procedure (can include repeat procedures) (Long-Term Effectiveness).

Additional Investigations (unpowered) include:

1. Total RF ablation time.

2. Total Radiation Exposure.

3. Repeat ablation procedure and associated hospitalizations.

4. Quality of Life, as measured by the EQ-5D and AFEQT.

5. Cost-effectiveness analysis.

2.4 Power and Sample Size Estimation

Since the primary objective of this study relates to the long-term effectiveness of FIRM-guided ablation versus conventional ablation for atrial fibrillation (AF), power and sample size estimates have been calculated relative to that endpoint only. We anticipate enrolling 77 subjects in each treatment arm, plus an additional 8 subjects per arm to account for possible drop-outs / lost to follow-ups, for a total of 170 subjects (in approximately 20 sites).

Description	Assumptions
FIRM Group Freedom from recurrence of AF at 3 months	.55
CONVENTIONAL Group Freedom from recurrence of AF at 3 months	.50
Probability of Type I error (α) (two-sided test)	.05

Minimum Total Sample Size (includes 10% adjustment for drop-outs and losses to follow-up)	170 (85 per group)

With 77 subjects in each group, the lower limit of the observed one-sided 95.0% confidence interval will be expected to exceed -0.150 with 80% power when the Standard proportion, p_C, is 0.500 and the Test expected proportion, p_F, is 0.550; results are based on 1000 simulations using the Newcombe-Wilson score method to construct the confidence interval. In order to account for potential drop-outs and losses to follow-up, an additional 10% (16) will be added to the total sample size, for a final sample size of 170 (85 per group).[3]

This power and sample size calculation was performed using NQuery 7.0 on the Microsoft Windows 10 operating system.

2.5   Missing Data and Lost to Follow-Up (Censoring)

No imputations or last observation carried forward (LOCF) will be conducted in this study. For purposes of the long-term primary safety and effectiveness endpoints, subjects missing safety or effectiveness data or lost to follow-up will be censored at their latest visit prior to the missing safety or effectiveness data.

For all other analyses, (acute safety and effectiveness), two presentations will be completed, one where the subject missing acute safety or effectiveness data or lost to follow-up will be excluded from the analysis, and another where that individual will be counted as a "failure" for the purpose of endpoint analysis. Both results will be presented.
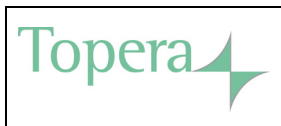
2.5.1   Handling of Screen Failures

Anticipated are two main types of screen failures. The first type will be screened by the clinical study site, and prior to randomization be classified as not eligible for inclusion into the study. The second type are subjects who fail entry criteria post-randomization, potentially while undergoing the procedure.

Screen failures will, at a minimum, have data collected reflecting completion of informed consent, demographic, and inclusion/exclusion criteria. If the screen failure occurred post-randomization, preparatory to undergoing the mapping/ablation procedure, these data will also be reflected in the clinical database.

Data on screen failures will be analyzed for any patterns observable as to demographic and inclusion/exclusion criteria, stratified by their randomization status and study site.

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[3] Newcombe RG (1988) Interval estimation for the difference between independent proportions: comparison of eleven methods. Statistics in Medicine 17:873-890.

2.6   Methods for Handling Multicenter Data

For the long-term primary safety and effectiveness endpoints, a Cox Proportional Hazards model will be fit, using center as a covariate to identify any potential site interaction with long-term safety and effectiveness outcomes. For acute safety and effectiveness endpoints, a Cochran-Mantel-Haenszel (CMH) test statistic will be calculated to evaluate the interaction of center on acute outcome.

2.7   Planned Interim Analyses

In order to maintain control over Type I error probability due to multiple primary endpoints, there will be NO interim analysis performed in this study.

2.8   Computer Systems and Statistical Analysis Software Packages

The following computer systems and statistical/reporting analysis software packages are anticipated:

- Microsoft Windows 10
- Mac OSX
- SAS
- DeltaGraph and DataGraph (on Mac OSX)
- Open Source "R" and appropriate open source packages

3 Tables, Listings, and Figures

3.1 Tables

3.1.1 Summary of Demographic Characteristics by Treatment Group

3.1.2 Summary of Index Ablation Procedure by Treatment Group

3.1.3 Summary of Acute Effectiveness by Treatment Group

3.1.4 Summary of Long-Term Effectiveness by Treatment Group

3.1.5 Summary of Acute Adverse Events by Treatment Group

3.1.6 Summary of All Adverse Events by Treatment Group

3.1.7 Summary of Acute Serious Adverse Events by Treatment Group

3.1.8 Summary of Change From Baseline of EQ5D Quality of Life Scale by Treatment Group

3.2 Listings

3.2.1 Listing of Subject Demographic Characteristics by Subject

3.2.2 Listing of Index Ablation Procedure by Subject

3.2.3 Listing of Adverse Events by Subject

3.2.4 Listing of Serious Adverse Events by Subject

3.2.5 Listing of EQ5D Quality of Life Scale by Subject

3.2.6 Listing of Retreatment Ablation Procedure by Subject

3.3 Figures

3.3.1 Kaplan-Meier Survival of Long-Term Safety by Treatment Group

3.3.2 Kaplan-Meier Survival of Long-Term Effectiveness by Treatment Group