# **R**andomized **E**uropean **A**trial **F**ibrillation study of **F**ocal **I**mpulse and **R**otor **M**odulation (REAFFIRM)

## Statistical Analysis Plan (SAP)

| | |
|---|---|
| PROTOCOL ID: | REAFFIRM - 01 |
| AUTHOR: | [redacted] |
| DATE: | August 5, 2014 |
| VERSION: | 01 |



[redacted]

## Table of Contents





[redacted]

[redacted]

# 1 INTRODUCTION

## 1.1 Study Overview

### 1.1.1 Title

REAFFIRM is a prospective randomized study to asses the safety and effectiveness of FIRM procedures followed by conventional ablation, including PVI (pulmonary vein isolation) versus a standard PVI ablation procedure for the treatment of symptomatic, persistent atrial fibrillation.

### 1.1.2 Objectives

The primary objective is to evaluate the safety and effectiveness of FIRM procedures for the treatment of symptomatic persistent (including long-standing persistent) atrial fibrillation (AF).

The secondary objective is to evaluate the treatment time and quality of life outcomes in subjects who undergo FIRM ablation.

### 1.1.3 Patient Population

REAFFIRM will include subjects experiencing at least two (2) documented episodes of symptomatic persistent atrial fibrillation (including long standing persistent) during the three (3) months preceding study entry. At least one episode should be documented by rhythm strip or ECG.

### 1.1.4 Inclusion Criteria

- Attempt of at least one Class I or III anti-arrhythmia drug with failure defined as recurrence of symptomatic atrial fibri8llation or adverse drug effect resulting in stopping the medication.
- Left atrial size suitable for mapping with existing basket catheters, currently ≤60mm on the largest diameter on CT scan or intracardiac echocardiography

### 1.1.5 Exclusion Criteria

- Class III or IV NYHA heart failure
- LVEF <35%
- Unrevascularized ischemia including symptomatic angina
- History of rheumatic heart disease
- History of intracardiac thrombus
- History of procedures that may complicate placement of a basket catheter
- Patients with a history of poor compliance
- Patients unwilling or unable to provide consent



[redacted]

### 1.1.6 Study Masking

REAFFIRM is an open-label, randomized study (no masking).

### 1.1.7 Randomization

REAFFIRM will be randomized 1 : 1, with half of the subjects allocated to the experimental group (FIRMap followed by conventional PVI ablation) and the other half to the control group (conventional PVI ablation only). Randomization will be accomplished during screening and entry into the ClinCapture EDC system being used for this study.

## 1.2 Study Outcomes

### 1.2.1 Primary Outcomes

#### *1.2.1.1 Acute Safety*

Freedom from major adverse events related to the procedure within seven (7) days of the procedure.

#### *1.2.1.2 Long Term Safety*

Freedom from cumulative major adverse events related to the procedure (including any repeat procedures required) within one year of the index procedure.

#### *1.2.1.3 Acute Effectiveness*

- The acute success of FIRM ablation is defined as elimination of the source as indicated by:
  - Source no longer noted on immediate post-ablation FIRMap AND
  - Anatomic (region designated by FIRMap ablated on electroanatomic mapping system) or electrical (reduction of electrogram amplitude to <0.2mV in region designated by FIRMap identified region

#### *1.2.1.4 Long Term Effectiveness*

- The long term success of FIRM ablation is defined as single procedure freedom from atrial fibrillation recurrence
  - Single procedure freedom from atrial fibrillation recurrence at 3 months
  - Subjects not achieving acute success at the index procedure, as defined above, will be considered long term success failures



[redacted]

#### *1.2.1.5 Secondary Outcomes*

##### 1.2.1.5.1 Quality of Life

EQ5D scores pre-ablation will be compared to those post-ablation at all time points separately and together (ANOVA).

##### 1.2.1.5.2 Reduction in AF Burden

In those subjects with CIEDs in place prior to the initial procedure, reduction in AF burden will be assessed using percent of AF in the 1-2 months prior to the initial procedure compared with percent of AF in the 3 month follow-up period.

##### 1.2.1.5.3 Total Ablation Time

Total 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.

##### 1.2.1.5.4 Total Radiation Exposure

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

##### 1.2.1.5.5 Repeat Procedure and Hospitalization

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

##### 1.2.1.5.6 Cardioversion for Early Recurrence of AF (ERAF)

Specific requirement for electrical cardioversion for AF/AT recorded in the first 3 month blanking period.

##### 1.2.1.5.7 Long-Term Freedom from all Atrial Arrhythmias

Freedom from recurrence of any atrial tachyarrhythmia (excluding typical CTI dependent atrial flutter) incuding AF at 3 months, and from 3 months after the initial AF ablation procedure.

##### 1.2.1.5.8 Cumulative Long-Term Freedom From AF

Cumulative long-term freedom from AF will be assessed at 12 months after the initial AF procedure but will permit results of repeat ablation.

##### 1.2.1.5.9 Early Recurrence of AF/AT

Recurrences of sustained AF/AT in the first 3 months.



[redacted]

#### 1.2.1.5.10 Change in Atrial Function

Change in left atrial size and pulmonary vein inflow Doppler on echocardiogram (when available).

#### 1.2.1.5.11 Change in Ventricular Function

Change in left ventricular ejection fraction and parameters of diastolic dysfunction (when available).

# 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 long-term effectiveness of FIRM ablation versus conventional ablation shall be defined as freedom from atrial fibrillation (AF) recurrence at 3 months. Freedom from AF recurrence is defined as no documented episodes of AF > 30 seconds with conventional non-invasive monitoring or, in the case of a cardiac implanted electronic device (CIED), < 1% AF noted overall.

The statistical hypothesis for this endpoint is operationalized as follows:

$H_O$: $p_E = p_C$

$H_A$: $p_E \neq p_C$

$\alpha$ = [redacted]

Where:

$p_E$ = the proportion of "successes" in the FIRMap arm

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

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



[redacted]

### 2.2.2 Acute Effectiveness (Secondary effectiveness endpoint)

The acute success of FIRM ablation is defined as elimination of the source as indicated by; 1) source no longer noted on immediate post-ablation FIRMap and; 2) anatomic (region designated by FIRMap ablated on electroanatomic mapping system) or electrical (reduction of electrogram amplitude to <0.2mV in region designated by FIRMap) ablation of the FIRMap identified region.

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:

$H_O$: $p_E = p_C$

$H_A$: $p_E \neq p_C$

$\alpha$ = [redacted]

Where:

$p_E$ = the proportion of "successes" in the FIRMap 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 major 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:

n = the total count of subjects presenting freedom from major 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:



[redacted]

$H_O$: $p_E = p_C$

$H_A$: $p_E \neq p_C$

$\alpha$ = [redacted]

Where:

$p_E$ = the proportion of "successes" in the FIRMap 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 cumulative major adverse events related to the procedure (including from any repeat procedures required) within one year of the index procedure.

The statistical hypothesis for this endpoint is operationalized as follows:

$H_O$: $p_E = p_C$

$H_A$: $p_E \neq p_C$

$\alpha$ = [redacted]

Where:

$p_E$ = the proportion of subjects free from major adverse events related to the procedure (including from any repeat procedures required) within one year of the index procedure in the FIRMap arm

$p_C$ = the proportion of subjects free from major adverse events related to the procedure (including from any repeat procedures required) 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 Power and Sample Size Estimation

[redacted]



[redacted]

[redacted]

## 2.4 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 Secondary Analyses

All secondary analyses will be for informational purposes only, and primarily descriptive in nature, and no statistical tests of significance will be performed.

## 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

No interim analyses are planned for 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
- Mac OSX
- SAS
- S-Plus



[redacted]

- 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



[redacted]