AtriCure, Inc.

STATISTICAL ANALYSIS PLAN

CONFIDENTIAL

EPi-Sense-AF
Protocol: VAL-1200(E)

Convergence of Epicardial and Endocardial RF Ablation
for the Treatment of Symptomatic Persistent AF

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TABLE OF CONTENTS

1 INTRODUCTION 6
2 STUDY OBJECTIVES, TREATMENTS, AND ENDPOINTS 6
2.1 Study Objectives 6
2.1.1 Primary Efficacy Objective 6
2.1.2 Primary Safety Objective 6
2.1.3 Secondary Objectives 6
2.1.4 Exploratory Objectives 7
2.2 Treatment Arm Comparisons 7
2.3 Study Endpoints 8
2.3.1 Primary Efficacy Endpoints 8
2.3.2 Secondary Efficacy Endpoints 9
2.3.3 Primary Safety Endpoint 9
2.3.4 Secondary Safety Endpoint 9
2.3.5 Exploratory Endpoints 9
3 STUDY DESIGN 10
3.1 Overall Study Design 10
3.2 Schedule of Study Assessments 12
4 SAMPLE SIZE CONSIDERATIONS 13
5 ANALYSIS POPULATIONS 14
5.1 Intent-to-Treat (ITT) Population 14
5.2 Modified Intent-to-Treat (mITT) Population 14
5.3 Per Protocol (PP) Population 14
5.4 Safety Population 14
6 CONSIDERATIONS FOR DATA ANALYSIS 15
6.1 Programming Environment 15
6.2 Strata and Covariates 15
6.3 Subgroups 15
6.4 Multiple Comparisons and Multiplicity 16
6.5 Significance Level 16
6.6 Statistical Notation and Methodology 16
7 DATA HANDLING METHODS 16
7.1 Missing Data 16
7.1.1 Date Values 16
7.2 Imputation of AF/ AFL/AT Freedom 17
7.3 Visit Windows 17
7.4 Data Derivations and Definitions 18
7.4.1 Baseline 18
7.4.2 Study Day, Blanking Period, and Time Points 18
7.4.3 Anti-Arrythmic Drugs 19
7.4.4 AF Freedom 20
7.4.5 AF/AFL/AT Freedom 21
7.4.6 Catheter Ablation 23
8 STUDY POPULATION 24
8.1 Subject Disposition 24
8.2 Informed Consent and Inclusion/Exclusion Criteria 24

8.3 Protocol Violations 24
8.4 Demographic and Other Baseline Characteristics 25
8.5 Medical History 25
8.6 Non-Study Medications 26
8.7 Pre-Procedure and Procedure Data 26
9 EFFICACY ANALYSES 26
9.1 Primary Efficacy Analysis 26
9.2 Multiplicity Adjustment 27
9.3 Sensitivity Analyses 29
9.3.1 Sensitivity Analyses on Analysis Populations 29
9.3.2 Tipping-Point Analysis 29
9.3.3 Geographical Differences 30
9.3.4 Multiple Imputation 30
9.4 Secondary Efficacy Analysis 32
9.4.1 ≥90% Reduction in AF Burden 32
9.4.2 SF-36 33
9.4.3 Atrial Fibrillation Severity Scale (AFSS) 35
9.4.4 Six Minute Walk Test 36
9.4.5 Freedom from Atrial Fibrillation 36
9.4.6 Freedom from Atrial Fibrillation, regardless of AADs 36
9.5 Exploratory Efficacy Analysis 36
9.5.1 Reduction from Baseline AF Burden at 18 Months 36
9.5.2 Change in Left Ventricular Ejection Fraction (LVEF) 37
9.5.3 Change in Left Atrial Size 37
9.5.4 Hospitalizations 37
9.5.5 Rhythm Disturbance Treatments 38
9.5.6 ≥75% Reduction in AF Burden 38
9.5.7 ≤12% Overall AF Burden 38
9.5.8 Freedom from AF/AFL/AT Requiring Intervention 39
9.5.9 Freedom from Stroke-Relevant AF/AFL/AT Duration 39
9.5.10 Conversion of Persistent to Paroxysmal AF 39
9.5.11 Time to First Episode of Persistent AF 39
10 SAFETY ANALYSES 39
10.1 Major Adverse Events (MAEs) 39
10.2 Adverse Events (AEs) 40
11 INTERIM ANALYSES 41
12 PLANNED STUDY ANALYSES 41
13 DEPARTURES FROM PROTOCOL-SPECIFIED ANALYSES 41
14 REFERENCES 42
15 ATTACHMENTS 43
15.1 Table of Contents for Data Displays 43
15.1.1 Tables and Figures 43
15.1.2 Listings 44

TABLE 1 STUDY DATA COLLECTION REQUIREMENTS 12
TABLE 2 CONTINUED LONG TERM DATA COLLECTION REQUIREMENTS 12

LIST OF ABBREVIATIONS

AAD	Anti-arrhythmic drug
AE	Adverse event
AF	Atrial fibrillation
AFB	Atrial fibrillation burden
AFL	Atrial flutter
ANCOVA	Analysis of covariance
AT	Atrial tachycardia
BMI	Body mass index (kg/m^2)
CRF	Case report form
CEC	Clinical Events Committee
CI	Confidence interval
CTCAE	Common Toxicity Criteria for Adverse Events
DC	Direct current
DRAE	Device-related adverse event
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
ICE	Intra-cardiac Echocardiograph
ITT	Intent to treat
LVEF	Left ventricular ejection fraction
MAE	Major adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
MRI	Magnetic resonance imaging
PP	Per Protocol
PT	Preferred term
PV	Pulmonary vein
QoL	Quality of life
SAE	Serious adverse event
SOC	System organ class
TEAE	Treatment-emergent adverse event
TEE	Trans-esophageal echocardiogram
TIA	Transient ischemic attack
TTE	Trans-thoracic echocardiogram

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of CONVERGE Protocol VAL-1200(E). Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection.

2 STUDY OBJECTIVES, TREATMENTS, AND ENDPOINTS

2.1 Study Objectives

The objectives of this randomized, open-label pivotal study are to evaluate the safety and efficacy of the EPi-Sense®-AF Guided Coagulation System with VisiTrax® (referred to in this document as EPi-Sense-AF procedure or convergent procedure) for the treatment of symptomatic persistent atrial fibrillation (AF) subjects who are refractory or intolerant to at least one Class I and/or III anti-arrhythmic drug (AAD) as compared to a standalone endocardial catheter ablation.

2.1.1 Primary Efficacy Objective

The primary objective is to demonstrate superiority of the experimental convergent procedure (EPi-Sense-AF) compared to the stand-alone endocardial catheter ablation (control) on overall success, defined as freedom from AF/AFL/AT (atrial fibrillation/atrial flutter/atrial tachycardia) absent Class I or III anti-arrhythmic drugs (AADs), except for previously failed Class I or III AADs with no increase in dosage, following the 3 month blanking period through the 12 months post-procedure follow-up visit.

2.1.2 Primary Safety Objective

The incidence rate of major adverse events (MAEs) in the treatment arm will be documented to demonstrate an acceptable risk profile.

2.1.3 Secondary Objectives

The secondary objectives are to demonstrate the efficacy of EPi-Sense-AF as:

- A 90% reduction in the subject's baseline AF burden (percent of time a subject is in AF) at 12 months post-procedure in the presence or absence of Class I/III AADs.
- Change in QoL measures from baseline to 12 months post-procedure.
- Change in six minute walk test scores from baseline to 12 months post-procedure.

2.1.4 **Exploratory Objectives**

The exploratory objectives are to:

- Demonstrate the efficacy of EPi-Sense-AF procedure as a 90% reduction in the subject's baseline AF burden at 18 months post-procedure, in the presence or absence of Class I/III AADs.
- Explore the impact of the EPi-Sense-AF convergent procedure on left atrial size.
- Explore the impact of the EPi-Sense-AF convergent procedure on left ventricular ejection fraction (LVEF).

In addition, the following may be evaluated for a health economics data analysis:

- Number of hospitalizations.
- Total number of days hospitalized.
- Number of rhythm disturbance treatments for a period of 12 months before and 6 to 18 months after the convergent procedure.

In addition, the following clinically relevant assessment for non-paroxysmal subjects from 2017 Heart Rhythm Society (HRS) guidelines will be evaluated, data permitting:

- Freedom from AF/AFL/AT requiring intervention (emergency visits, cardioversion, urgent care visit, re-ablation, etc.).
- Significant reduction in AF burden: 75% reduction from pre- to post-ablation, evaluated at 6 and 12 months.
- Total post-ablation burden of 12%, evaluated at 6 and 12 months.
- Freedom from stroke-relevant AF/ AFL/AT-duration (cutoff of 1 hour).
- Regression of AF: conversion of persistent to paroxysmal AF.
- Prevention in AF progression: time to first episode of persistent AF.

2.2 Treatment Arm Comparisons

The EPi-Sense-AF Guided Coagulation System with VisiTrax will be compared to a standalone endocardial catheter ablation for the treatment of symptomatic persistent AF in subjects who are refractory or intolerant to at least one Class I and/or III AAD.

The test procedure is the minimally invasive "EPi-Sense-AF" procedure using the device, EPi-Sense-AF Guided Coagulation System with VisiTrax combined with an open irrigated radiofrequency ablation catheter to complete pulmonary vein isolation by ablating breakthroughs between the epicardial lesions. The EPi-Sense-AF is able to coagulate cardiac tissue from the epicardial surface, allowing the procedure to be performed on a beating heart, endoscopically without chest incisions, lung deflation, or dissections of the pericardial reflections (attachments between the pericardium and atrium).

The reference or control procedure is standard standalone endocardial "catheter ablation" described in Attachment B of the protocol.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoints

The primary efficacy endpoint is success or failure to be AF/AT/AFL free absent class I and III AADs except for a previously failed or intolerant class I or III AAD with no increase in dosage following the 3 month blanking period through the 12 months post procedure follow-up visit.

Subjects will be considered primary efficacy failures if any of the following conditions are observed:

- Any electrocadiographically documented AF/AFL/AT episode of 30 sec duration or longer by Holter, event monitor or rhythm strip; or for the full 10 second recording of a standard 12 lead ECG following the 3 month blanking period through the 12 months post procedure follow-up visit.

- The use of a new or an increase in the dose of a previously failed class I or class III AAD following the 3 month blanking period through the 12 months post procedure follow-up visit.

- DC cardioversion for AF/AFL/AT following the 3 month blanking period through the 12 months post procedure follow-up visit.

- Subsequent left-sided catheter ablation for AF/AFL/AT at anytime during the 12 months post procedure follow-up visit.

- Catheter ablation for right-sided typical atrial flutter following the 3 month blanking period through the 12 months post procedure follow-up visit.

As described in Section 7.4.2, the blanking period is the period from index procedure through 3 months post-procedure visit.

2.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Success or failure to achieve a 90% reduction from baseline AF burden and off all Class I and III AADs at 12 months post-procedure.
- Success or failure to achieve a 90% reduction from baseline AF burden regardless of their Class I and III AAD status at 12 months post-procedure.
- Change in SF36 Quality of Life (QoL) scale scores and composite scores from baseline values to 12 months post-procedure.
- Change in University of Toronto Atrial Fibrillation Symptom Scale (AFSS) composite score from baseline values to 12 months post-procedure.
- Change in distance walked during the 6 minute walk test from baseline values to 12 months post-procedure.
- Success or failure to be AF free and off all Class I and III AADs except for a previously failed or intolerant Class I or III AAD with no increase in dosage following the 3 month blanking period through the 12 months post-procedure follow-up visit.
- Success or failure to be AF free, regardless of Class I and III AAD status following the 3 month blanking period through the 12 months post-procedure follow-up visit.

2.3.3 Primary Safety Endpoint

The primary safety endpoint is defined as the incidence of MAEs (listed in Section 10.1 and defined in Section 1.5.3 of the study protocol) for subjects undergoing the convergent procedure (EPi-Sense-AF) for the procedural to 30- day post-procedure time period. All MAEs will be adjudicated by the Clinical Events Committee (CEC), thus maintaining the objectivity of the primary safety endpoint.

2.3.4 Secondary Safety Endpoint

The secondary safety endpoint for the study will be the incidence of serious adverse events (SAEs) in the study through the 12 month post-procedure visit, in each treatment arm of the study.

2.3.5 Exploratory Endpoints

The exploratory endpoints are:

- Success or failure to achieve a 90% reduction from baseline AF burden with and without Class I/III AADs at 18 months post-procedure.

- Change in left ventricular ejection fraction (LVEF).
- Atrial remodeling assessed by a decrease in left atrial size.
- Health Economics Data
    - Change in number of hospitalizations and total number of days hospitalized for the 12 months post-procedure period (6 months to 18 months post-procedure) compared to the number of hospitalizations in the 12 months prior to the procedure.
    - Change in rhythm disturbance treatments (e.g. electrical or pharmacological cardioversion, AAD therapy, supraventricular ablative therapy) 12 months post-procedure period (6 to 18 months post-procedure) compared to 12 months prior to the procedure.

Additional exploratory endpoints, pending availability and usability of appropriate data, will include:

- Freedom from AF/AFL/AT requiring intervention (emergency visits, cardioversion, urgent care visit, re-ablation, etc.).
- Significant reduction in AF burden: 75% reduction from pre- to post-ablation, evaluated at 6 and 12 months.
- Total post-ablation burden of 12%, evaluated at 6 and 12 months.
- Freedom from stroke-relevant AF/ AFL/AT-duration (cutoff of 1 hour).
- Regression of AF: conversion of persistent to paroxysmal AF.
- Prevention in AF progression: time to first episode of persistent AF.

3 STUDY DESIGN

3.1 Overall Study Design

This study is a prospective, open-label, 2:1 randomized (convergent procedure [EPi-Sense-AF] versus stand-alone endocardial catheter ablation [catheter ablation]), multi-center pivotal clinical study. The study will enroll and randomize one hundred and fifty three (153) subjects from up to thirty (30) sites, approximately twenty-seven (27) in the United States and three (3) international sites.

Subjects in both arms of the study will be evaluated post-procedure at 7 days; 1, 3, 6, and 12 months; a long-term follow-up visit at 18 months; and long-term phone follow-ups at 2, 3, 4, and 5 years.

The study design includes a pre-procedure period (screening/baseline assessments within 90 days of the planned procedure, randomization, and pre-procedure [intra-op exclusion] visit); the procedure visit (day 0); a post-procedure follow-up period (including a 3-month blanking period); and a long-term follow-up period. The study design is illustrated in Table 1. Refer to Table 1 and Table 2 for further details.

Table 1 Study Data Collection Requirements

	Baseline	Pre-procedure	Procedure	7 Days	1 month	3 months	6 months	12 months
Informed Consent for Study Participation	X							
Inclusion/Exclusion Criteria	X	X	X					
Medical History	X							
Spiral CT or MRI	X						X	
Procedure			X					
ECG	X		X		X	X	X	X
ECHO (TTE)	X			X			X	
ECHO (TEE)		X						
24 hr Holter monitor	X						X	X
Documentation of any AF treatments					X	X	X	X
Medications (selected)	X		X	X	X	X	X	X
Evaluation of AEs			X	X	X	X	X	X
Six minute walk test	X							X
QoL assessments	X							X

Note: TTE=trans-thoracic echocardiogram; TEE=trans-esophageal echocardiogram. QoL assessments include SF-36 and AFSS.

Table 2 Continued Long Term Data Collection Requirements

	18 months	Phone Follow-up 2 years	Phone Follow-up 3 years	Phone Follow-up 4 years	Phone Follow-up 5 years
Health Status	X	X	X	X	X
ECG	X				
Rhythm Status	X	X	X	X	X
7 day Holter monitor	X				
Medications (selected)	X	X	X	X	X
Evaluation of AEs	X	X	X	X	X

3.2 Schedule of Study Assessments

Pre-Procedure Period:

Subjects meeting enrollment criteria described in protocol sections 4.2-4.4, who have agreed to study participation and signed the informed consent, will be considered enrolled in the study. Baseline evaluations will then be completed to further determine study procedure eligibility, as described in protocol section 4.5. These baseline assessments (i.e., the Baseline Visit) must be completed within 90 days of the study procedure.

Randomization will be implemented using Tempo™, the electronic research tool used for collecting clinical data. Randomization will be blocked by investigator site on randomly chosen blocks of 3 or 6 patients allocated 2:1 to the treatment arms, respectively. Appropriate randomization codes will be provided on the screen immediately after randomization for a subject is requested. The treatment arm code will be automatically stored in the study
database.

A trans-esophageal echocardiograph (TEE) or intra-cardiac echocardiograph (ICE) will be performed immediately pre-procedure for intra-op exclusion purposes (i.e., Pre-Procedure Visit). If the subject meets either of the intra-op exclusion criteria specified in protocol section 5.1, the subject will not undergo a study procedure.

Patients becoming ineligible for a study procedure as a result of meeting the study intra-op exclusion criteria will be replaced. They will be followed for 30 days post-TEE or post-ICE, and information collected will be included in the study listings.

Study Procedure (Day 0):

Once the procedure intra-op exclusion conditions have been evaluated, and the subject is determined to be eligible to proceed with the study, the study procedure will be scheduled and performed. See the protocol sections 5.2 and 5.3 for a more detailed description of each treatment arm procedure.

Post-Procedure Follow-up Assessments:

Subjects are evaluated at 7 days (7 days + 7 days post-procedure), 1 month (30 days + 7 days post-procedure), 3 months (90 days ± 15 days post-procedure), 6 months (180 days ± 30 days post-procedure), and 12 months (365 days ± 30 days post-procedure). A long-term follow-up visit is also conducted at 18 months (day 550 ± 30 days post-procedure) and long-term phone follow-up at 2, 3, 4, and 5 years (± 30 days) post-procedure. In all cases, post-procedure refers to the index (study) procedure.

The period from index procedure through the 3-month post-procedure visit will be considered a blanking period, as described in Section 7.4.2. During this time, the use of AADs, cardioversions, and any recurrence or episodes of AF will not be considered a treatment failure. Subjects who receive AF therapy following the 3 month blanking period through the 12 months post-procedure follow-up visit will be considered primary efficacy failures, as described in Sections 7.2 and 9.1.

4 SAMPLE SIZE CONSIDERATIONS

A sample size of 153 subjects is planned for this study, which is based on the primary endpoint of AF/AFL/AT freedom.

It is assumed that the success rate for the control arm (catheter ablation) is 40%,

and the study is designed to document superiority of EPi-Sense-AF with a 65% success rate. The sample size result, based on 2-sided α = .05, 80% power, a 2:1 allocation of EPi-Sense-AF:catheter ablation, and a 10% drop out rate, is 102:51 or 153 subjects.

5 ANALYSIS POPULATIONS

All subjects meeting inclusion/exclusion criteria will be considered enrolled subjects. Those not meeting all inclusion/exclusion criteria will be considered screen failures. Randomized subjects will include all subjects randomized to a treatment arm. Summaries of all subjects (such as those for disposition) will include both enrolled subjects and screen failures.

5.1 Intent-to-Treat (ITT) Population

The ITT population will include all subjects who receive a randomized study procedure (either EPi-Sense-AF or catheter ablation). This population will be used as the primary analysis population for efficacy analyses. Subjects will be analyzed according to randomized treatment.

5.2 Modified Intent-to-Treat (mITT) Population

The mITT population will include all subjects who receive a randomized study procedure (either EPi-Sense-AF or catheter ablation) and have at least one post-procedure follow-up visit after the 3 month blanking period (as described in Section 7.4.2) with non-missing efficacy results. This follow-up visit is defined as a visit with echocardiogram, rhythm disturbance evaluation, or Holter monitor results, after the end of the blanking period. This population will be used to support efficacy analyses. Subjects will be analyzed according to randomized treatment.

5.3 Per Protocol (PP) Population

The PP population will include all subjects who receive a randomized study procedure (either EPi-Sense-AF or catheter ablation) who have at least four of the five first year visits (that is, at least 4 of the 7 day, 1 month, 3 months, 6 months, and 12 months visits are completed) and who have no major protocol violations or deviations. This population will be used for sensitivity analysis of the primary efficacy analysis.

A blinded list of all protocol deviations will be provided to the Medical Monitor to be categorized (major or minor) prior to study unblinding and database lock, as described in Section 8.3.

Subjects will be analyzed according to randomized treatment.

5.4 Safety Population

The Safety population will include all subjects who receive a randomized study

procedure (either EPi-Sense-AF or catheter ablation). Subjects will be analyzed according to procedure received, in the event it differs from the randomized procedure. This population will be used for all safety analyses.

6 CONSIDERATIONS FOR DATA ANALYSIS

6.1 Programming Environment

All analyses will be conducted using SAS® version 9.3 or higher.

6.2 Strata and Covariates

There are no planned stratified analyses or adjustments for covariates, other than the subgroup analyses specified in Section 6.3 and potential adjustments for geographical location discussed in Section 9.3.3. Additional subgroup analysis and covariate adjustments will be performed as necessary.

6.3 Subgroups

A subgroup analysis of the primary endpoint will be conducted for the subgroup variables of:

- Geographic location - Europe, Region of United States (such as West, Southeast, Northeast, Central/Midwest) as per SAP section 9.3.3.
- Gender (M vs F).
- Age at baseline visit (<65 vs ≥ 65 years).
- Body mass index (BMI; <30 vs ≥ 30 kg/m^2) at baseline visit,
- Access type (transdiaphragmatic or sub-xyphoid, which will be collected from source documentation, entered in a spreadsheet, finalized prior to database lock, and incorporated into analysis datasets).
- Left atrium size (< median value vs ≥ median value, as recorded on the Pre-Procedure echocardiogram, based on the median of the ITT population). Other clinically relevant cut-points may be defined prior to unblinding the study.
- Left atrial volume (<median value vs ≥ median value, as recorded on the CT Scan or MRI at the Baseline visit, based on the median of the ITT population). Other clinically relevant cut-points may be defined prior to unblinding the study.
- AF classification (Persistent versus Long-standing persistent AF).

For each of these, a logistic regression model will be fit to the primary endpoint, modeling for (1) treatment arm, (2) subgroup variable (dichotomous), and (3) interaction term of treatment arm * subgroup variable. A two-tailed alpha level of 0.15 will be used for determining poolablity of results. If the p-value of the interaction

term and subgroup variable are both >0.15, the subgroup variable will be considered to not have significant impact and the subgroups will be pooled. If either is $p \leq 0.15$, the primary analysis will be presented for each level of that subgroup.

6.4 Multiple Comparisons and Multiplicity

Planned adjustments for multiplicity are described in Section 9.2.

6.5 Significance Level

Unless otherwise noted, all statistical analyses will be conducted with a significance level (α) of 0.05 and utilize two-sided testing.

6.6 Statistical Notation and Methodology

Unless stated otherwise, the term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation (SD), minimum (min), and maximum (max) for continuous data and frequencies and percentages for categorical data. Min and max values will be rounded to the precision of the original value, means and medians will be rounded to 1 decimal place greater than the precision of the original value, and SDs will be rounded to 2 decimal places greater than the precision of the original value. Percentages will be rounded to the nearest whole number (zeros are not displayed) with values of "< 1%" and "> 99%" shown as necessary for values falling near the boundaries. P-values will be presented with 3 decimal places and values less than 0.001 will be presented as < 0.001.

Unless otherwise noted, all data collected during the study will be included in data listings and will be sorted by treatment arm, subject number and then by date/time for each subject.

7 DATA HANDLING METHODS

7.1 Missing Data

Every effort will be made to obtain the protocol-specified data for all study assessments at each scheduled visit for all subjects.

7.1.1 Date Values

In cases of incomplete dates (e.g., pertaining to AE, concomitant medication, medical history, etc.), the missing component(s) will be assumed as the most conservative value(s) possible, as follows. Date imputation will only be used for computational purposes, such as calculation of study day, determination of prior versus concomitant medications, and determination of treatment-emergent adverse events. Actual date values, as they appear in the original eCRFs, will be displayed in listings.

Date	Possible Date Range	Impute as…	Reason
Start Date	Definitely before date of procedure	Earliest possible date	Longest possible duration
Start Date	Before or after date of procedure, depending on imputation	Impute as earliest possible date, on or after date of procedure	Greatest potential causality
Start Date	Definitely after date of procedure	Earliest possible date	Longest possible duration
End Date	Any	Latest possible date	Longest possible duration

7.2 Imputation of AF/ AFL/AT Freedom

Subjects who were randomized and received study procedure but have no post-treatment assessments will be conservatively imputed as having failed to achieve freedom from AF/ AFL/AT (e.g., treatment failure). Similarly, subjects who were randomized and received study procedure but do not have treatment assessments following the 3-month blanking period (as described in Section 7.4.2), or a visit was performed but insufficient information was collected to determine whether or not AF/AFL/AT was experienced and/or whether Class I/III AADs were administered, will also be imputed as treatment failures. Subjects who do not have complete information for the efficacy evaluation period (for example, withdrew before 12 months) but have sufficient information to conclude that they would be classified as *not* AF/AFL/AT free (such as: new or increased dose of Class I/III AAD or documented findings of AF/AFL/AT) will be considered treatment failures. These subjects will *not* be considered to have been imputed, for the purpose of tipping point or multiple imputation analyses, as it is clear that they would have been treatment failures even if complete information had been collected.

The same approach will be utilized to impute AF freedom for secondary efficacy analyses.

A tipping-point analysis will also be performed, as described in Section 9.3.2, which will be performed on un-imputed data. Further details on criteria for treatment failure are provided in study protocol Section 1.5.

7.3 Visit Windows

All data will be listed according to the nominal visit obtained from the CRF. Visits will also be assigned an analysis visit, used for data summaries and analyses, based on visit

windowing.

Section 3.2 defines the tolerance range for each follow-up visit. A visit that occurs outside the specified range will be categorized as an unscheduled visit, and excluded from summaries and analyses. If an additional visit was not performed within that visit window, the visit will be identified as a protocol violation. That is, an unscheduled visit will be windowed to the nearest visit, but will not be considered a protocol deviation if the regularly scheduled visit occurred within its window.

If more than one visit falls within a given visit window for a subject:

- If only one visit has non-missing data, the data from the visit with non-missing data will be assigned to that analysis visit, and used for summaries and analyses.
- If >1 visit has non-missing data, the data from the latest visit within the window will be assigned to that analysis visit, and used for summaries and analyses.

7.4 Data Derivations and Definitions

The following definitions and derivations will be used for this study.

7.4.1 Baseline

The baseline value will be the last non-missing value collected before study treatment. This may be collected at the Baseline visit, Pre-Procedure visit, or an unscheduled visit.

Change from baseline will be calculated as observed value – baseline value. Percent change from baseline will be calculated as change from baseline divided by the baseline value, multiplied by 100.

7.4.2 Study Day, Blanking Period, and Time Points

Relevant assessments (e.g. Rhythm Disturbance Evaluation) which do not have a specific date on the CRF page will be assigned the date for that study visit. Inclusion of that assessment in the analyses of study endpoints will be based on whether that visit date falls within the efficacy evaluation window. Other assessments (ECG, Holter monitor, etc.) will be included or excluded based on the date recorded on the specific CRF page.

- Day 1 will be considered the date of study procedure. Study day will be computed as Date – Study Procedure Date + 1 for assessments or events on or after the date of procedure, and as Date – Study Procedure Date for assessments or events prior to the date of procedure.
- The 3 month blanking period is defined as the time from the date of study

procedure until 3 months post-procedure. If the subject's 3 month visit is within the visit window specified in Section 3.2 (90 days ± 15 days), the day of the 3 month visit will be the last day of the blanking period. If the nominal 3 month visit is not performed but an unscheduled visit falls within that visit window and is categorized as the 3 month visit per Section 7.3, the day of that visit will be the last day of the blanking period. If multiple unscheduled visits fall within that window (and there is no nominal 3 month visit), the unscheduled visit (with sufficient efficacy data to determine if a subject was AT/AF/AFL free) closest to the 90 day mark will be used to determine the end of the blanking period. If a subject does not have a visit within the 3 month window, the blanking period will end on the 90th day after study procedure.

- Similarly, the 12 month post-procedure visit (as defined for the end of the efficacy evaluation period) will be determined as follows. If the subject's 12 month visit is within the visit window specified in Section 3.2(365 days ± 30 days), the day of the 12 month visit will be used. If the nominal 12 month visit is not performed but an unscheduled visit falls within that visit window and is categorized as the 12 month visit per Section 7.3, the day of that visit will be used. If multiple unscheduled visits fall within that window (and there is no nominal 12 month visit), the unscheduled visit closest (with sufficient efficacy data to determine if a subject was AT/AF/AFL free) to the 365 day mark will be considered the 12 month post-procedure visit for this purpose. If a subject does not have a visit within the 12 month window, but has subsequent study visits or other criteria such that it is necessary to define a date for the hypothetical 12 month visit, the 365th day after the study procedure will be used.
- If necessary, the 1 month visit, 6 month visit and 18 month long-term follow-up visit date will be defined as necessary for efficacy purposes using the approach spelled out for the 12 month visit.

7.4.3 **Anti-Arrythmic Drugs**

Class I/III AADs will include Quinidine, Procainamide, Disopyramide, Lidocaine, Phenytoin, Mexiletine, Tocainide, Flecainide, Propafenone, and Moricizine (Class I AADs) as well as Amiodarone, Sotalol, Ibutilide, Dofetilide, Dronadarone, and E-4031 (Class III AADs). Prior to database lock, a list of all medications (both prior and concomitant) taken by subjects who have received a study procedure will be provided to the Medical Monitor or designee for review. This list will not include subject identifiers or treatment arm. The Medical Monitor or designee will indicate which medications should be categorized as Class I or III AADs. This information will be finalized prior to database lock and subsequent unblinding of study sponsor, and incorporated into analysis datasets. If desired, a list of previously failed Class I/III AADs as recorded at the Baseline visit may also be provided to the monitor or designee for reference.

7.4.4 **AF Freedom**

A subject will be considered **AF free** for a time period if the subject:

- Does not exhibit AF
- Has sufficient efficacy assessments to determine that AF was not present
- Does not meet failure criteria (including the use of new Class I/III AADs or increased dose of a previously failed Class I/III AAD). Criteria for treatment failure is provided in the study protocol section 1.5.

If a subject exhibits AF or meets failure criteria, the subject will be classified as **not AF free** for that time period. If a subject has insufficient efficacy assessments and does not meet failure criteria, and does not exhibit AF on any efficacy assessments during that period, the subject will be classified as **indeterminate**, and subject to imputation as described in Sections 7.2 and 9.3.

Does not exhibit AF is defined as:

Subject has no atrial fibrillation, where atrial fibrillation is defined as a Holter monitor finding or ECG rhythm of 'AF' or 'Other' with description including atrial fibrillation, where the Holter monitor date or ECG date falls within that period. (Note that findings of AF/AFL/AT without specific information that AF is present will not be considered demonstration of AF).

A list of descriptions for 'Other' results from the Holter monitor and ECG will be tabulated and provided to the Medical Monitor or designee to determine whether the description is indicative of the subject having AF. This tabulation will not include subject identifiers or treatment arm. Additional information collected on the Holter monitor, ECG, or Rhythm Disturbance Evaluation eCRF from that visit may also be provided to help with classification. This information will be finalized prior to database lock and subsequent unblinding of study sponsor, and incorporated into analysis datasets in order to determine if subjects meet criteria for to be AF free at a given assessment, and hence determine if the subject is AF free for a given period of time.

Has sufficient efficacy assessments to determine that AF was not present is defined as:

A subject must have either Holter monitor, ECG, or Rhythm Disturbance Evaluation results indicating no AF at each scheduled visit within that period (for example, both 6 & 12 month visits, for the period after the blanking period through the 12 month visit), in order to be considered AF free for that period.

Does not meet failure criteria (including the use of new Class I/III AADs or increased dose of a previously failed Class I/III AAD) is defined as not having any of the following:

- The use of a new or an increase in the dose of a previously failed Class I/III AAD

during the time period. Previously failed Class I/III AADs, and their dose and units, are recorded as part of AF documentation at the Baseline visits. All Class I/III AADs used during this time period, which do not clearly match one of the failed AADs by name and dose level, will be considered a new medication or increased dose. If there is any ambiguity in determining if an AAD is the same as one previously failed (i.e., the trade name is listed in one location and the generic name in another), the Medical Monitor or designee will be consulted and such characterization finalized prior to database lock and subsequent unblinding of study sponsor.

- Cardioversion during the time period. Any electrical cardioversion or pharmacologic cardioversion recorded on the Rhythm Disturbance Evaluation eCRF during this time period will be considered a treatment failure.
- Subsequent left-sided catheter ablation at any time during the 12 months post-procedure follow-up visit, as defined in Section 7.4.2. This will be determined by the presence of an endocardial catheter ablation recorded on the rhythm disturbance evaluation eCRF where the date performed is equal to the 12 month visit date. Catheter ablation location (left, right, or other/indeterminate) will be determined as described in Section 7.4.6. (Right-sided catheter ablation for atrial flutter will not be considered a failure to meet AF freedom).

7.4.5 **AF/AFL/AT Freedom**

A subject will be considered AF/AFL/AT free for a time period if the subject:

- Does not exhibit AF, AFL, or AT
- Has sufficient efficacy assessments to determine that AF, AFL, and AT were not present
- Does not meet failure criteria (including the use of new Class I/III AADs or increased dose of a previously failed Class I/III AAD)

If a subject exhibits AF, AFL, or AT or meets failure criteria, the subject will be classified as **not AF/AFL/AT free** for that time period. If a subject has insufficient efficacy assessments and does not meet failure criteria, and does not exhibit AF/AFL/AT on any efficacy assessments during that period, the subject will be classified as **indeterminate**, and subject to imputation as described in Sections 7.2 and 9.3. Further details on criteria for treatment failure are provided in study protocol section 1.5.

<u>Does not exhibit AF, AFL, or AT is defined as:</u>

- Has no atrial fibrillation, where atrial fibrillation is defined as a Holter monitor finding or ECG rhythm of ‘AF’ or ‘Other’ with description including atrial

fibrillation, where the Holter monitor date or ECG date falls within that period.

- Has no atrial flutter, where atrial flutter is defined as a Holter monitor finding or ECG rhythm of 'Typical AFL (Right Atrial)' or 'Atypical AFL (Left Atrial)' or 'Other' with description including atrial flutter, where the Holter monitor date or ECG date falls within that period.
- Has no atrial tachycardia, where atrial tachycardia is defined as a Holter monitor finding or ECG rhythm of 'AT' or 'Other' with description including atrial tachycardia, where the Holter monitor date or ECG date falls within that period.
- Has a Rhythm Disturbance Evaluation eCRF where 'any symptomatic AF/AFL/AT episodes' is marked No or Unknown at each visit where completed.
- Has a Holter monitor eCRF where the number of >30 second AF/AFL/AT episodes is 0 for each eCRF page where the Holter monitor date falls within that period.

A list of descriptions for 'Other' results from the Holter monitor and ECG will be tabulated and provided to the Medical Monitor or designee to determine whether the description is indicative of the subject having AF/AFL/AT. This tabulation will not include subject identifiers or treatment arm. Additional information collected on the Holter monitor, ECG, or Rhythm Disturbance Evaluation eCRF from that visit may also be provided to help with classification. This information will be finalized prior to database lock and subsequent unblinding of study sponsor, and incorporated into analysis datasets in order to determine if subjects meet criteria for to be AF/AFL/AT free at a given assessment, and hence determine if the subject is AF/AFL/AT free for a given period of time.

Has sufficient efficacy assessments to determine that AF, AFL, and AT were not present is defined as:

A subject must have either Holter monitor, ECG, or Rhythm Disturbance Evaluation results indicating no AF/AFL/AT at each scheduled visit within that period (for example, both 6 & 12 month visits, for the period after the blanking period through the 12 month visit), in order to be considered AF/AFL/AT free for that period.

Does not meet failure criteria (including the use of new Class I/III AADs or increased dose of a previously failed Class I/III AAD) is defined as not having any of the following:

- The use of a new or an increase in the dose of a previously failed Class I/III AAD during the time period. Previously failed Class I/III AADs, and their dose and units, are recorded as part of AF documentation at the Baseline visits. All Class I/III AADs used during this time period, which do not clearly match one of the

failed AADs by name and dose level, will be considered a new medication or increased dose. If there is any ambiguity in determining if an AAD is the same as one previously failed (i.e., the trade name is listed in one location and the generic name in another), the Medical Monitor or designee will be consulted and such characterization finalized prior to database lock and subsequent unblinding of study sponsor.

- Cardioversion for AF/AFL/AT during the time period. Any electrical cardioversion or pharmacologic cardioversion recorded on the Rhythm Disturbance Evaluation eCRF during this time period will be considered a treatment failure.
- Subsequent left-sided catheter ablation for AF/AFL/AT at any time during the 12 months post-procedure follow-up visit, as defined in Section 7.4.2. This will be determined by the presence of an endocardial catheter ablation recorded on the rhythm disturbance evaluation eCRF where the date performed is equal to the 12 month visit date. Catheter ablation location (left, right, or other/ indeterminate) will be determined as described in Section 7.4.6.

- Catheter ablation for right-sided typical atrial flutter during the time period. This will be determined by the presence of an endocardial catheter ablation recorded on the Rhythm Disturbance Evaluation eCRF where the date performed falls within the time period of interest. Catheter ablation location (left, right, or other/indeterminate) will be determined as described in Section 7.4.6. Catheter ablation for right-sided typical atrial flutter will be categorized as those marked as being performed for "Other SVT" where the location is categorized as right side, or performed for "Typical AFL (Right Atrial)".

7.4.6 **Catheter Ablation**

Catheter ablation date and location(s) (as a free text field) are collected on the Rhythm Disturbance Evaluation eCRF page. Prior to database lock and subsequent unblinding of study sponsor, a list of ablation locations will be tabulated and provided to the Medical Monitor or designee for categorization of ablation location. Possible categorizations will include: Left, Right, Other, or Indeterminate. This list will not include subject identifiers or treatment arm. This information will be finalized prior to database lock, and incorporated into analysis datasets in order to determine if subjects meet criteria for treatment failure based on left or right side cardiac ablations as specified in Section 9.1.

8 STUDY POPULATION

Unless otherwise noted, the Safety Population will be used for summaries of the study population.

8.1 Subject Disposition

Subject disposition will be presented for all subjects. The subject disposition listing will include the date of study completion (at approximately 12 months post treatment) or withdrawal, whether the study was completed per protocol (for both main study period and long-term follow-up), reason for withdrawal, date of last contact, and documentation of attempts to contact the subject. The listing of analysis populations will include whether the subject was included in each analysis population and the reason for exclusion. The number of subjects in each population, number of subjects who completed the study, number of subjects who discontinued from the study, number of intra-op exclusion failures, and reasons for study discontinuation will be summarized.

8.2 Informed Consent and Inclusion/Exclusion Criteria

The informed consent listing will include whether the informed consent was completed appropriately, date of informed consent, and protocol version date. The inclusion/exclusion criteria listing will include whether or not the subject was eligible to participate, inclusion/exclusion criteria failed, whether or not the subject qualified for randomization, and randomized treatment arm.

8.3 Protocol Violations

Protocol violations/deviations will be recorded on the eCRF, and categorized as inclusion/exclusion criteria, informed consent issue, out of window visit, protocol-required evaluation not completed, or other (with additional information specified). The date of the violation, description, and corrective action (if applicable) will also be recorded.

Prior to database lock and subsequent unblinding of study sponsor, a list of violations will be provided to the Medical Monitor or sponsor designee for determination of major protocol violations. The designations of major or minor violation will be finalized prior to database lock and subsequent unblinding of study sponsor, and incorporated into analysis datasets. Major protocol violations will be identified in data listings.

Protocol violations (both major and minor) and major protocol violations will be summarized by category and treatment arm.

8.4 Demographic and Other Baseline Characteristics

The demographics and baseline characteristics listing will include date of birth, age, gender, race, ethnicity, height, weight, body mass index (BMI), presence of persistent AF vs long-standing persistent AF, and smoking history (never smoked, past smoker, current smoker, unknown).

Gender, ethnicity, race, BMI, and smoking history will be summarized descriptively by treatment arm and overall. Age, weight, and height will each be summarized continuously by treatment arm and overall.

Demographics and baseline characteristics of subjects with missing data will be compared between the two treatment arms, as well as to those subjects without missing data, to explore whether there are any factors associated with having missing data. Gender, ethnicity, race, age, persistent vs. long-standing persistent AF, and BMI will be compared between the treatment arms, separately for subjects whose AT/AF/AFL freedom needs to be imputed as per Section 7.2 (i.e. those with missing information for the primary efficacy endpoint) and those whose information is not missing. Fisher's exact test will be used to compare gender, ethnicity, and persistent AF. Race will also be compared using the Fisher's Exact test, with subjects grouped into White or Non-white categories. Age and BMI will be compared using a Student's t-test or the Wilcoxon rank sum test. Smoking history (treating unknown values as missing) will be compared using the chi-square test.

Demographic and baseline characteristics will similarly be compared between those with missing information for the primary endpoint (those having an indeterminate result for AF/AFL/AT status, as described in Section 7.4.5; imputation as described in Section 7.2 will not be applied for this comparison) and those without, after pooling treatment arms within each of the two groups.

8.5 Medical History

Medical history will be listed by subject and body system. The number of subjects with any medical history will be summarized for overall medical history and by body system, by treatment arm and overall.

Cardiac history will be listed by subject, date, and aneurysm location (if applicable). The number of subjects with cardiac history will be summarized by cardiac history type, by treatment arm and overall.

Cardiac interventions will be listed by subject, procedure, and date.

Cardioversion history over the previous 12 months will be listed by subject, date, and cardioversion type. The number of cardioversions during that period will be summarized by cardioversion type, by treatment arm and overall.

Documentation of persistent AF and other AF history will be listed by subject. The number of years in AF, and AF associated symptoms over the last 12 months will be summarized by treatment arm and overall.

8.6 Non-Study Medications

All class I, II, III, and IV AADs, as well as other cardiac and anti-coagulants taken by the subject prior to and during study enrollment, will be recorded on the eCRF. All recorded non-study medications that are halted prior to the study procedure date will be classified as prior medications. Medications taken on or after the date of study procedure, including those taken both before and after the procedure, will be categorized concomitant. If insufficient information is available to definitively categorize a medication, it will be considered concomitant. No standardized classification of medications (such as using a drug dictionary) is currently planned.

All medications will be listed by subject. Prior medications will be indicated in the listing. Class I/III AADs will also be flagged in data listings, as well as presented in a separate listing. No summaries of medications will be presented.

8.7 Pre-Procedure and Procedure Data

Different pre-procedure and procedure data are collected for subjects in each treatment arm. Therefore, these listings will be presented separately for subjects in each treatment arm. Subjects undergoing pre-procedure assessments, who discontinue prior to study procedure, will be included in study listings, and flagged as not having undergone study procedure. Similar, summaries of pre-procedure and procedure data will be presented separately by treatment arm, where applicable.

9 EFFICACY ANALYSES

The ITT population will be used as the primary analysis population for efficacy analyses. The m ITT and PP populations will be used for sensitivity analyses as described. Efficacy summaries and analyses will be presented by treatment arm.

In case of sparsity of cells (when the table consists of a cell where the expected number of frequencies is fewer than 5), Fisher's Exact test will be utilized instead the chi-square test for a 2x2 table for the primary and secondary efficacy endpoints.

9.1 Primary Efficacy Analysis

The binary primary endpoint of success or failure to achieve freedom from AF/AT/AFL absent class I and III AADs except for a previously failed or intolerant class I or III AAD with no increase in dosage following the 3 month blanking period through the 12 months post procedure follow-up visit will be compared between the two treatment groups using a chi-square test using a two-sided alpha of 0.05 to determine if superiority of the treatment arm is attained. This is detailed in Sections 2.3.1 and 7.4.5 of the SAP.

The analysis will be performed on the ITT population. If necessary, imputation will be performed as specified in Section 7.2.

Define P as the true percentage of subjects failing to achieve AF/AFL/AT freedom, where P_T is the true failure rate for the treatment arm and P_C for the control arm. The hypothesis to test is:

$$H_0: P_T = P_C \quad \text{vs} \quad H_a: P_T \neq P_C$$

The formula for the chi-square test is:

$$\chi^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

where O_i represents the number of observed events in the i^{th} cell and E_i represents the expected number of events in the i^{th} cell. H_0 is rejected in favor of H_A if the resulting p-value <0.05 and the estimated P_T exceeds P_C. If $E_i < 5$ for any cell (that is, if the [number of subjects in a treatment arm * total number of successes / total number of subjects] is <5, or similarly for the number of failures), then the Fisher's Exact test will be used in lieu of the chi-square test.

If the $p \leq 0.05$, we will conclude that the percentages differ significantly between treatment arms.

The number and percent of subjects achieving AF/AFL/AT freedom will be summarized by treatment arm, and individual results listed by subject.

The primary efficacy analysis will be repeated on the specific subgroups as described in Section 6.3.

9.2 Multiplicity Adjustment

The fixed-sequence procedure[1,2] will be used to evaluate the following secondary endpoints. Each of these tests will be tested at the same significance level (α=0.05) in this predetermined order. Each endpoint is only tested if the prior endpoint is successful ($p \leq 0.05$). This procedure does not inflate the Type I error rate since the sequence is prospectively specified and no further testing is performed once an endpoint in the sequence fails to show significance ($p > 0.05$)[2]. All tests will be performed on the ITT population. If sufficient data have not been collected during this study to permit the evaluation of a given endpoint, that endpoint should be skipped and the subsequent endpoint evaluated:

1) Achievement of ≥90% reduction in baseline AF burden at 12 months post-procedure, where subjects with new or increased dosage of Class I/III AADs during the efficacy evaluation period are categorized as not achieving ≥90% reduction, using the Fisher's Exact test as described in Section 9.4.1.

2) AF freedom during efficacy evaluation period, using the chi-square or Fisher's Exact test as described in Sections 9.4.5 and 9.1, where subjects with new or increased dosage of Class I/III AADs during the efficacy evaluation period are categorized as not achieving AF freedom.

3) Achievement of ≥90% reduction in baseline AF burden at 12 months post-procedure, regardless of Class I/III AAD usage, using the Fisher's Exact test as described in Section 9.4.1.

4) AF freedom during efficacy evaluation period, using the chi-square or Fisher's Exact test as described in Sections 9.4.5 and 9.1, regardless of Class I/III AAD usage.

5) Change in AFSS composite score at 12 months post-procedure, using an ANCOVA model as described in Section 9.4.3.

6) Change in SF-36 physical health composite score at 12 months post-procedure, using an ANCOVA model as described in Section 9.4.2.

7) Change in SF-36 mental health composite score at 12 months post-procedure, using an ANCOVA model as described in Section 9.4.2.

8) Change in distance walked during six-minute walk test at 12 months post-procedure, using an ANCOVA model as described in Section 9.4.4.

9) Change in left ventricular ejection fraction (LVEF) at 6 months post-procedure, as described in Section 9.5.2.

10) Atrial remodeling assessed by a decrease in left atrial size at 6 months post-procedure, as described in Section 9.5.3.

11) Freedom from AF/AFL/AT requiring intervention (emergency visits, cardioversion, urgent care visit, re-ablation, etc.), data permitting.

12) Achievement of ≥75% reduction in baseline AF burden at 12 months post-procedure, where subjects with new or increased dosage of Class I/III AADs during the efficacy evaluation period are categorized as not achieving ≥75% reduction, using the Fisher's Exact test as described in Section 9.4.1.

13) Achievement of no more than 12% AF burden at 12 months post-procedure, where subjects with new or increased dosage of Class I/III AADs during the efficacy evaluation period are categorized as not achieving ≤ 12% AF burden, using the Fisher's Exact test as described in Section 9.4.1.

14) Freedom from stroke-relevant AF/ AFL/AT-duration (cutoff of 1 hour), data permitting.

15) Regression of AF: conversion of persistent to paroxysmal AF, data permitting.

16) Prevention in AF progression: time to first episode of persistent AF, data permitting.

Multiplicity tests #1-16 are based on the 12 month data analyses, and will be performed at that time. The following multiplicity tests are based on data collected at the 18 month visit. Therefore, they will be performed after data collection and cleaning is completed for the 18 month visit. As described above, these endpoints will only be evaluated using the fixed-sequence procedure if all of the prior endpoints are significant.

17) Success or failure to achieve a 90% reduction from baseline AF burden with and without Class I/III AADs at 18 months post-procedure, where subjects with new or increased dosage of Class I/III AADs during the efficacy evaluation period are categorized as not achieving ≥90% reduction, as described in Section 9.5.1.

18) Change in number of hospitalizations for the 12 months post-procedure period (6 months to 18 months post- procedure) compared to the number of hospitalizations in the 12 months prior to the procedure, as described in Section 9.5.4, date permitting.

19) Change in rhythm disturbance treatments (e.g. electrical or pharmacological cardioversion, AAD therapy, supraventricular ablative therapy) 12 months post-procedure period (6 to 18 months post-procedure) compared to 12 months prior to the procedure, as described in Section 9.5.5, data permitting.

9.3 Sensitivity Analyses

9.3.1 Sensitivity Analyses on Analysis Populations

The primary efficacy analysis will be repeated on the mITT and PP populations. If appropriate, Fisher's Exact test will be used in lieu of the chi-square test. The imputation methods described in Section 7.2 will be utilized for the analysis where appropriate.

9.3.2 Tipping-Point Analysis

A tipping-point analysis [3] will be conducted to explore the sensitivity of the results to the effect of missing data. To summarize, a tipping-point analysis evaluates the necessary difference in the number of events (for binary data) between treatment arms in the cohort of missing subjects at which the study conclusion is changed. For example, if each treatment arm had 20 subjects with missing data for treatment success/failure, a tipping-point analysis would start by assuming that 0/20 subjects in each treatment arm failed to achieve AF/AFL/AT freedom, and calculate the chi- square (or Fisher's Exact) test statistic. Then this would be repeated with 1, 2, 3 … 20/20 subjects in one treatment arm, while the other treatment arm is held at 0/20 subjects. The second treatment arm is then increased to 1, 2, 3 … 20/20 subjects (while the first arm is 0, 1 … 20), so that every combination of number of failures among subjects with missing data across the two arms was compared. The "tipping point" is the point at which the p-value crosses the α=.05 line. It is often summarized as "X more

treatment failures among the subjects with missing data in Arm A than those in Arm B" and can be displayed graphically as well. This information can then be used to evaluate the impact of the missingness, and how reasonable it might be for that pattern of data to have occurred if there were no missing data.

The tipping-point analysis will be performed on the primary efficacy analysis, using both the mITT and ITT populations (without the imputation method described in Section 7.2). The results will be displayed graphically, similar to Figure 1 of Yan, Li and Nan[3].

9.3.3 **Geographical Differences**

The primary efficacy analysis may be repeated with pooled sites or regions as a covariate, to explore potential differences between geographic areas, using the ITT population.

9.3.4 **Multiple Imputation**

The primary efficacy analysis will be repeated on the ITT population, using multiple imputation to impute AF/AFL/AT freedom for subjects in who it was missing. Subjects who do not have complete information for the efficacy evaluation period, but have sufficient information to conclude that they would be classified as treatment failures, will be considered treatment failures and not imputed. The imputation will be limited to subjects in the ITT population.

The logistic regression method in SAS (version 9.3 or higher) will be used to impute AF/AFL/AT freedom, such as in the following pseudocode:

```
PROC MI data=xxx seed=xxxx out=xxx nimpute=5;
  CLASS free ;
  FCS LOGISTIC (free = var1 var2 var3 var4);
  VAR var1 var2 var3 var4 free;
  run;
```

The covariates used may include the following. Other covariates may be specified as necessary:

- Demographic and baseline covariates
- Whether a 3 month visit was performed within window vs. not performed or performed out of window. An unscheduled visit falling within the window, which has sufficient information recorded for the ECG, Holter monitor, or rhythm disturbance evaluation to determine whether or not a subject is AF/AFL/AT free, will be treated as having the scheduled visit performed in window. (If all subjects in the ITT population have the visit performed within window, this covariate is not necessary).

- Whether the 6 month visit was performed within window vs. not performed or performed out of window. An unscheduled visit falling within the window, which has sufficient information recorded for the ECG, Holter monitor, or rhythm disturbance evaluation to determine whether or not a subject is AF/AFL/AT free, will be treated as having the scheduled visit performed in window. (If all subjects in the ITT population have the visit performed within window, this covariate is not necessary).
- AF burden (%) at baseline visit.
- SF-36 physical and mental health composite scores at baseline visit.
- AFSS composite score at baseline visit.
- Six-minute walk test distance walked (meters) at baseline visit.
- Total days of hospitalization in the 12 months prior to study procedure.
- Number of years in AF.
- Transdiaphragmatic vs sub-xyphoid access type.
- Left atrial size (at baseline) – to be dichotomized as per SAP section 6.3 if necessary.
- Left atrial volume (at baseline) – to be dichotomized as per SAP section 6.3 if necessary.
- Investigational site
- Geographic location - Europe, Region of United States (such as West, Southeast, Northeast, Central/Midwest) as per SAP section 9.3.3
- Persistent AF vs long standing persistent AF

From this list of covariates (and any other covariates included as necessary), the following shall be included as covariates in the imputation model, based on Section 2.2.1 of Berglund and Heeringa[1]:

- Any demographic or baseline characteristics that are statistically significant between subjects with missing AF/AFL/AT freedom and subjects without that information missing (e.g., age, gender, ethnicity, race [white vs. non-white], height, weight, BMI, or smoking history) as described in Section 8.4 and presented in a summary table.
- Any demographic or baseline characteristics that are statistically significant between treatment arms as described in Section 8.4 and presented in a summary table.
- Any other covariate which is associated with AF/AFL/AT freedom, as determined by using Fisher's Exact test (for dichotomous covariates), Cochran-Mantel-Hanszel test

(for nominal or ordinal covariates), or Wilcoxon rank sum test (for continuous covariates), based on the subjects in the ITT population who are not being imputed.

- Any other covariate which is associated with a missing primary endpoint, as determined by using Fisher's Exact test (for dichotomous covariates), Cochran-Mantel-Hanszel test (for nominal or ordinal covariates), or Wilcoxon rank sum test (for continuous covariates), based on the subjects in the ITT population. That is, an indicator variable will be created to summarize whether a subject's AF/AFL/AT freedom is being imputed, and any covariate which is associated with that indicator variable will be retained.
- Any key analysis variables as determined by AtriCure (such as: left atrial size at baseline, number of years in AF, and geographic region)

If the resulting list of covariates results in an over-specified model or other statistical convergence issues, covariates will be removed until there is no longer a statistical issue. Covariates will be removed starting with obviously redundant variables (for example, height, weight, and BMI all being in the model) and then beginning with those which have the least relationship between the covariate and either the missingness indicator variables or AF/AFL/AT freedom. Key analysis variables will be retained throughout unless any of that group of covariates causes such issues, in which case they will be removed in an order discussed with the sponsor.

Five data imputation sets will be imputed using PROC MI as outlined above. The primary analysis will be performed separately for each of the imputation sets, and the results combined using PROC MIANALYZE. Those results will be presented in a summary table.

9.4 Secondary Efficacy Analysis

All secondary analyses will be perfomed on the ITT population. These analyses may be repeated on the mITT and PP populations.

9.4.1 ≥90% Reduction in AF Burden

The AF burden, as a percentage, is recorded on the Holter Monitor eCRF. The recorded values and percent change from baseline in AF burden will be summarized by time point at 6, 12, and 18 months post-procedure.

The percent change from baseline at 12 months will be categorized as ≥90% reduction (percent change ≤ -90%) or <90% reduction (percent change >-90%). The proportion of subjects achieving ≥90% reduction at 12 months will be compared between treatment arms using Fisher's Exact test.

This analysis will be repeated for the following subsets of subjects:

- Subjects who have taken a Class I/III AAD during the efficacy evaluation period (excluding previously failed Class I/III AADs with no increase in dosage).

- Subjects who have *not* taken a Class I/III AAD during the efficacy evaluation period (excluding previously failed Class I/III AADs with no increase in dosage).

- Subjects who have taken any Class I/III AAD during the efficacy evaluation period.

No imputation will be performed for missing data.

These analysis (on all subjects and the three subsets) will also be repeated where subjects with a new or increased dosage of Class I/III AADs during the efficacy evaluation period will be categorized as not having achieved ≥90% reduction. This will be performed on the ITT population. No imputation will be performed for missing data.

9.4.2 **SF-36**

The SF-36[4,5] is administered at the Baseline and 12 month visits. The SF-36 collects items across the physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health scales. Those scales are then combined into 2 overall summary measures, for physical health and mental health. Item scores are summed (after reverse coding the 10 items requiring it) to form the raw scale scores, which are rescaled to a 0-100 scale and standardized using a z-score transformation based on SF-36 scale means and standard deviations from the general U.S. population, as provided in the scoring manual[2,3]. Aggregate scores for the physical and mental health components are then calculated using weighted averages of the standardized scale scores, and standardized into the physical and mental health component scores using a T-score transformation to have a mean of 50 and a standard deviation of 10. Lower scores reflect poorer quality of life.

The algorithm from scoring manual[2,3] is provided as follows for ease of reference but [2,3] remains the definitive reference.

The raw scale scores are calculated as follows, where missing values (as long as <50% of item scores are missing) are imputed as the mean score of the other item scores, after any recoding of those scores has been performed:

- **Physical Functioning:** #3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j – sum of scores, where ≥5 item scores are non-missing.
- **Role-Physical:** #4a, 4b, 4c, 4d – sum of scores, where ≥2 item scores are non-missing.
- **Bodily Pain:** #7, 8 – sum of scores, where at least 1 item score is non-missing:
    - #7 recoded, 1 → 6.0, 2 → 5.4, 3 → 4.2, 4 → 3.1, 5 → 2.2, 6 → 1.0
    - #8 recoded, based on item score and original (pre-coded) score for

item #7: if score for #7 and #8 are both 1, recode #8 to 6; if score for #7 is 2 – 6 and score for #8 is 1, recode #8 to 5; if score for #8 is 2 – 5 and item #7 is non-missing, recode #8 to (6-score). If item #7 is missing, recode #8 to: 1 → 6.0, 2 → 4.75, 3 → 3.5, 4 → 2.25, 5 → 1.0.

- **General Health:** #1, 11a, 11b, 11c, 11d – sum of scores, where ≥3 item scores are non-missing.
  - #1 recoded, 1 → 5.0, 2 → 4.4, 3 → 3.4, 4 → 2.0, 5 → 1.0.
  - #11a and #11c: not recoded.
  - #11b and #11d: recoded as 6 – score.
- **Vitality:** #9a, 9e, 9g, 9i – sum of scores, where ≥2 item scores are non-missing.
  - #9a and #9e: recoded as 7 – score.
  - #9g and #9i: not recoded.
- **Social Functioning:** #6, 10 – sum of scores, where at least 1 item is non-missing and #6 is reverse coded using 6 – score and #10 is not recoded.
- **Role-Emotional:** #5a, 5b, 5c – sum of scores, where ≥2 item scores are non-missing.
- **Mental Health:** #9b, 9c, 9d, 9f, 9h – sum of scores, where ≥3 item scores are non-missing.
  - #9b, #9c and #9f: not recoded.
  - #9d and #9h: recoded as 7 – score.

The scores are then recalibrated into transformed scale scores using the formula 100* ((actual raw score – lowest possible raw score) / possible raw score range), to rescale them to a 0-100 scale. Specifically, the transformed scores are calculated as:

- Physical Functioning (PF): 100* ((actual raw scale score - 10) / 10)
- Role-Physical (RP): 100* ((actual raw scale score – 4) / 4)
- Bodily Pain (BP): 100* ((actual raw scale score - 2) / 10)
- General Health (GH): 100* ((actual raw scale score – 5) / 20)
- Vitality (VT): 100* ((actual raw scale score – 4) / 20)
- Social Functioning (SF): 100* ((actual raw scale score – 2) / 8)
- Role-Emotional (RE): 100* ((actual raw scale score – 3) / 3)
- Mental Health (MH): 100* ((actual raw scale score – 5) / 25)

Each of the raw scale scores is then adjusted by the specific mean and standard deviation for that scale to create a standardized scale score:

- PF_Z = (PF – 84.52404) / 22.89490

- RP_Z = (RP – 81.19907) / 33.79729
- BP_Z = (BP – 75.49196) / 23.55879
- GH_Z = (GH – 72.21316)/ 20.16964
- VT_Z = (VT – 61.05453) / 20.86942
- SF_Z = (SF – 83.59753) / 22.37642
- RE_Z = (RE – 81.29467) / 33.02717
- MH_Z = (MH – 74.84212) / 18.01189

The physical and mental health component scores are created from the standardized scale scores, weighted by specific factor score coefficients. If any of the scale scores are missing, the component score will also be missing:

- Physical health component aggregate score (AGG_PHYS) = 0.42402*PF_Z + 0.35119*RP_Z + 0.31754*BP_Z + 0.24954*GH_Z + 0.02877*VT_Z – 0.0073*SF_Z – 0.19206*RE_Z – 0.22069*MH_Z
- Mental health component aggregate score (AGG_MENT) = -0.22999*PF_Z - 0.12329*RP_Z – 0.09731*BP_Z – 0.01571*GH_Z + 0.23534*VT_Z + 0.26876*SF_Z + 0.43407*RE_Z + 0.48581*MH_Z

The scores are then transformed to the norm-based (50, 10) scoring as follows:

- Physical health component score (PCS) = 50 + AGG_PHYS*10
- Mental health component score (MCS) = 50 + AGG_MENT*10

The transformed scale scores (on a 0-100 scale) and norm-based component scores, and their changes from baseline, will be summarized by time point and treatment arm. Raw item scores, as well as transformed scale scores and norm- based component scores will be listed by subject.

The changes from baseline at 12 months will be analyzed using an analysis of covariance (ANCOVA) model with the scale or component score as the dependent variable, and treatment arm and baseline scale or component score as covariates.

9.4.3 **Atrial Fibrillation Severity Scale (AFSS)**

The University of Toronto's AF Severity Scale is also administered at the Baseline and 12 month visits. An overall subject-perceived severity score will be created by taking the mean of the results from item #7 (severity of most recent episode of irregular heart rhythm) and item #8 (severity of first episode of irregular heart rhythm), both scored as 1 = not at all severe and 10 = extremely severe. A composite score for total AF burden will be calculated by adding overall severity score to the result from item #5 (average frequency of AF, scored from 1=continuous to 11=less than once a year) and the result from item #6 (average duration of AF, scored from 1=continuous to 8=a few minutes), resulting in a range of possible scores from 3 – 29.

This calculation was described previously[6] although Dorian et al erroneously stated the possible score range as 3-30. If any of the item results making up either the subject-perceived severity score or the composite score is missing, that score will also be missing.

Individual item results, as well as the composite score, will be listed by subject and time point. The results for items #4 (global well-being, scored 1-10), #5 (AF frequency), and #6 (AF duration), as well as the overall severity score and composite score will be summarized by time point and treatment arm, as will their change from baseline.

The changes from baseline at 12 months will be analyzed separately for each of those five scores using an ANCOVA model with the score as the dependent variable, and treatment arm and baseline score as covariates.

9.4.4 Six Minute Walk Test

A six minute walk test will also be administered at the Baseline and 12 month visits. The distance walked (in meters) will be assessed, as will the number of laps completed and whether the subject stopped or paused before 6 minutes. The level of shortness of breath and level of fatigue will be assessed both pre- and post-test on a 0-10 scale.

All collected information will be listed by subject and time point. The distance walked at each visit, and change from baseline in distance walked, will be summarized by time point and treatment arm. The change from baseline in distance walked at 12 months will be analyzed using an ANCOVA model with the distance walked as the dependent variable, and treatment arm and baseline distance walked as covariates.

9.4.5 Freedom from Atrial Fibrillation

Freedom from atrial fibrillation will be analyzed as described for the primary efficacy endpoint, using the ITT, mITT, and PP populations. Freedom from AF is defined in Section 7.4.4. Imputation of AF freedom, as described in Section 7.2, will be utilized.

9.4.6 Freedom from Atrial Fibrillation, regardless of AADs

Freedom from atrial fibrillation, regardless of AADs, will be analyzed as described for the primary efficacy endpoint. Freedom from AF is defined in Section 7.4.4; this analysis will not consider the use of new or increased doses of Class I/III AADs to be treatment failure. Imputation of AF freedom, as described in Section 7.2, will be utilized where appropriate.

9.5 Exploratory Efficacy Analysis

9.5.1 Reduction from Baseline AF Burden at 18 Months

The reduction in AF burden from baseline to 18 months will be categorized and analyzed as described for the reduction in AF burden at 12 months (Section 9.4.1).

This analysis will be performed on the ITT population. No imputation will be performed for missing data.

9.5.2 Change in Left Ventricular Ejection Fraction (LVEF)

The left ventricular ejection fraction, defined as a percentage, will be evaluated via echocardiography at the Baseline and 6 month visits. The change from baseline in LVEF will be analyzed using an ANCOVA model with the LVEF as the dependent variable, and treatment arm and baseline LVEF as covariates.

9.5.3 Change in Left Atrial Size

The size of the left atrium, in centimeters, will be evaluated via echocardiography at the Baseline and 6 month visits. The change from baseline in left atrial size will be analyzed using an ANCOVA model with the left atrial size as the dependent variable, and treatment arm and baseline left atrial size as covariates.

9.5.4 Hospitalizations

Hospitalizations will be recorded including start date, duration, and reason for hospitalization (cardiovascular, AF, other). All information will be listed by subject and date. The number of hospitalizations and total number of days hospitalized will be summarized by treatment arm as follows:

- Hospitalizations in the 12 months prior to study procedure (defined hospitalizations with start dates on or after the 365th day before the study procedure, and before the study procedure date.
- Hospitalizations for the 12 month period beginning on the day after the 6 month visit (see Section 7.4.2) through the 365th day after the 6 month visit.

The change in the number of hospitalizations between the two periods will be calculated for each subject as the number of hospitalizations in the 6-18 month period minus the number of hospitalizations in the 12 months prior to the study procedure. The change in the total number of days hospitalized will be calculated similarly. The change will not be calculated for subjects who withdraw from the study within 18 months after study procedure, and they will be excluded from analyses. No imputation will be performed.

The difference between treatment arms in the change in the number of hospitalizations will be analyzed using a Poisson model with treatment arm and the number of hospitalizations in the 12 months prior to the study procedure as covariates. The difference between treatment arms in the change in the total number of days hospitalized will be analyzed similarly. Both analyses will be performed on the ITT population.

9.5.5 Rhythm Disturbance Treatments

Rhythm disturbance treatments are defined as cardioversion (either electrical or pharmacological), AAD therapy, endocardial catheter ablation, or convergent procedure. The dates of treatments, as recorded on the Rhythm Disturbance Evaluation eCRF, will be used to determine the type and date of occurrence. The number of rhythm disturbance treatments will be summarized by treatment arm as follows:

- Rhythm disturbance treatments in the 12 months prior to study procedure (defined hospitalizations with start dates on or after the 365th day before the study procedure, and before the study procedure date.
- Rhythm disturbance treatments for the 12 month period beginning on the day after the 6 month visit (see Section 7.4.2) through the 365th day after the 6 month visit.

The change in the number of rhythm disturbance treatments between the two periods will be calculated for each subject as the number of rhythm disturbance treatments in the 6-18 month period minus the number of rhythm disturbance treatments in the 12 months prior to the study procedure. The change will not be calculated for subjects who withdraw from the study within 18 months after study procedure, and they will be excluded from analyses. No imputation will be performed.

The difference between treatment arms in the change in the number of rhythm disturbance treatments will be analyzed using a Poisson model with treatment arm and the number of rhythm disturbance treatments in the 12 months prior to the study procedure as covariates. This analysis will be performed on the ITT population.

9.5.6 ≥75% Reduction in AF Burden

The percent change from baseline at 12 months will also be categorized as ≥75% reduction (percent change ≤ -75%) or <75% reduction (percent change >-90%). The proportion of subjects achieving ≥75% reduction at 12 months will be compared between treatment arms using Fisher's Exact test, as described in Section 9.4.1.

This analysis will be repeated for the subsets of subjects described for the analysis of 90% reduction of AF burden. No imputation will be performed for missing data.

9.5.7 ≤12% Overall AF Burden

Subjects will be categorized as having no more than 12% AF burden or >12% AF burden at 6, 12, and 18 months. The proportion of subjects with >12% AF burden will be compared between treatment arms using Fisher's Exact test, as described in Section 9.4.1.

This analysis will be repeated for the subsets of subjects described for the analysis of

90% reduction of AF burden. No imputation will be performed for missing data.

9.5.8 Freedom from AF/AFL/AT Requiring Intervention

Freedom from AF/AFL/AT requiring intervention (emergency visits, cardioversion, urgent care visit, re-ablation, etc.) will be analyzed as described for the primary efficacy analysis, data permitting. Further details of the analysis will be finalized pending availability and usability of appropriate data.

9.5.9 Freedom from Stroke-Relevant AF/AFL/AT Duration

Freedom from stroke-relevant AF/AFL/AT duration (cutoff of 1 hour) will be analyzed as described for the primary efficacy analysis, data permitting. Further details of the analysis will be finalized pending availability and usability of appropriate data.

9.5.10 Conversion of Persistent to Paroxysmal AF

Conversion of persistent to paroxysmal AF will be analyzed for the ITT population, data permitting. Further details of the analysis will be finalized pending availability and usability of appropriate data.

9.5.11 Time to First Episode of Persistent AF

Time to first episode of persistent AF will be analyzed for the ITT population, data permitting. Further details of the analysis will be finalized pending availability and usability of appropriate data.

10 SAFETY ANALYSES

The Safety Population will be used for all summaries of safety assessments. No formal testing of statistical hypotheses will be performed on safety endpoints.

10.1 Major Adverse Events (MAEs)

MAEs (listed below and defined in Section 1.5.3 of the study protocol) will be adjudicated by the CEC. These adjudicated events will be recorded in a spreadsheet following the committee meeting and provided to the sponsor or designee after each meeting. The complete list of adjudicated events will be finalized prior to database lock and incorporated into an analysis dataset, separate from the adverse event dataset. MAEs will be summarized by event type and treatment arm, based on onset date:

- Date of study procedure through the 30th day post-procedure
- 31st day post-procedure through 12 months (365th day) post-procedure
- Overall

The MAEs for this study are as follows:

- Cardiac tamponade/perforation

- Severe pulmonary vein stenosis
- Excessive bleeding
- Myocardial infarction
- Stroke
- Transient ischemic attack
- Atrioesophageal fistula
- Phrenic nerve injury
- Death

The primary safety analysis will be to document an acceptable risk profile. This criterion will be defined as an acceptable level of MAEs. It is estimated that the true incidence rate for MAEs in this study population is no more than 12%. A 95% one-sided confidence interval for the investigational treatment arm based on a 102 subject sample size is 5%, resulting in an upper bound of MAEs being less than 20%. This result would document an acceptable risk profile for the investigational arm.

10.2 Adverse Events (AEs)

All reported terms (investigator descriptions) for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. Treatment-emergent AEs (TEAEs) will be defined as AEs starting on or after the day of the study procedure. Relationship to EPi-Sense_AF device, relationship to endocardial catheter system, and relationship to study treatment/procedure, all reported as not related, unlikely related, possibly related, probably related, or definitely related, will be categorized as related (probably, possibly, or definitely), or unrelated (unlikely or not related).

All summaries of TEAEs will be presented by event type or system organ class (SOC) (as collected on the eCRF) and, for those in 'Other' event type, by SOC, preferred term (PT), and by treatment arm. Subjects will be counted at most 1 time per event type, SOC, or PT. Events will be summarized at the maximum severity or highest reported relationship, where applicable. The following summaries will be presented:

- TEAEs
- TEAEs with onset through the 30th day after study procedure
- Treatment-emergent serious adverse events (SAEs)
- Severe TEAEs
- TEAEs leading to discontinuation from the study
- TEAEs related to study treatment/procedure
- TEAEs related to endocardial catheter system
- TEAEs related to study device
- TEAEs by severity

All AEs will be listed by subject, event type, SOC, PT, verbatim term, and onset

date. Additional listings will be provided for SAEs, AEs leading to discontinuation, AEs leading to death, and unanticipated adverse device effects (UADE).

11 INTERIM ANALYSES

There are no planned interim analyses. Ad hoc analyses may be performed from time to time as necessary for regulatory agencies, safety review, corporate planning, etc. No adjustments to p-values in the final analyses will be made for such ad hoc analyses.

12 PLANNED STUDY ANALYSES

An analysis of the primary efficacy and safety endpoints, and additional other analyses performed on the data collected through the 12 month visit, will be performed after all subjects have completed their 12 month visit or discontinued. The data collected through the 12 month visit will be cleaned, quality checked, and frozen or locked prior to this analysis. All tables, listings, and figures will be produced at this time, even though some listings will only include limited data, such as the Long-Term Follow Up listing and analysis of hospitalization data, which compares occurrences in the 12 months prior to study procedure to those 6-18 months post-procedure.

A subset of the tables, listings, and figures may be produced after all subjects have completed their 18 month visit or discontinued. The data collected at the 18 month visit, and any unscheduled visits between the 12 and 18 month visits, will be cleaned and quality checked and frozen prior to this analysis. This subset is expected to include outputs related to concomitant medications, adverse events, hospitalizations, ECGs, and AF burden.

In addition, a subset of the tables, listings, and figures may be produced at intervals (for example, yearly) during the long-term follow-up period. This subset is expected to include the outputs related to long-term follow up.

The final analysis will be conducted after the last subject completes the 5 year follow-up visit or discontinues the study. This analysis will focus on the results from the long-term follow up data, but will also incorporate data collected earlier in the study. The remaining data will be cleaned and quality checked, and the entire database locked, prior to this analysis.

13 DEPARTURES FROM PROTOCOL-SPECIFIED ANALYSES

Protocol section 5.1 states that subjects who met intra-op exclusion criteria will be followed for 30 days post procedure (post-TEE or post-ICE) and will be included in the study safety analysis only. The Safety Population is defined as subjects who receive study procedure (EPi-Sense-AF or catheter ablation). Because subjects who meet intra-op exclusion criteria do not undergo a study procedure, they are not included in the

Safety Population and therefore, are not included in safety summary analyses. Instead, they will be included in data listings.

The mITT population has been clarified from the original text of including all study subjects who receive a randomized procedure and have at least one post-treatment follow-up visit, to state that it all randomized subjects who have at least one post-procedure follow-up visit after the 3 month blanking period, with non-missing efficacy results. The PP population definition has been clarified to state that having at least four of the five first year visits means at least four of the: 7 day, 1 month, 3 month, 6 month, and 12 month visits.
Protocol section 9.4 states that subjects who were randomized but have no post- blanking period assessments will be conservatively imputed as therapeutic failures at six months. Treatment success or failure is evaluated for the 3 to 12-month time period overall and not evaluated at the 6-month period specifically. Therefore, subjects who were randomized but have no post-blanking period assessments are imputed as therapeutic failures as described in Section 7.2, but are not specifically imputed as failure at 6 months.

Direct current (DC) cardioversion is listed as criteria for treatment failure in the protocol. The SAP expands that definition to include both electrical and pharmacologic cardioversion.

14 REFERENCES

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[3] Yan X, Lee S, Li N. Missing data handling methods in medical device trials. JNL Biopharm Stat 2009,19(6):1085-1098.

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[5] Ware, JE Jr, Kosinski M, Keller D. (1993) SF-36 Physical and Mental Health Summary Scales: A User's Manual. 8. 23-28. Downloaded from https://www.researchgate.net/publication/292390260_SF-36_Physical_and_Mental_Health_Summary_Scales_a_User%27s_Manual on July 10, 2018.

[6] Dorian P et al. Quality of life improves with treatment in the Canadian Trial of Atrial Fibrillation. Am Heart J 2002, 143(6): 984-990.

15 ATTACHMENTS

15.1 Table of Contents for Data Displays

The primary efficacy analysis will be performed using the ITT, mITT, and PP populations, as described in Section 9.1. The remaining efficacy analyses will be produced for the ITT population. They may also be produced for the mITT and PP populations if desired. Table numbering has been assigned to allow for the creation of these additional tables in sequence.

15.1.1 Tables and Figures

Table 14.1.1	Summary of Subject Disposition All Subjects
Table 14.1.2	Summary of Protocol Violations and Deviations Safety Population
Table 14.1.3.1	Summary of Demographic and Baseline Characteristics Safety Population
Table 14.1.3.2	Summary of Demographic and Baseline Characteristics Comparison Among Subjects with Missing Data for the Primary Efficacy Endpoint
Table 14.1.3.3	Summary of Demographic and Baseline Characteristics Comparison Between Subjects with Missing and Non-Missing Data
Table 14.1.4	Summary of Medical History Safety Population
Table 14.1.5	Summary of Cardiac History Safety Population
Table 14.1.6	Summary of Cardioversion History Safety Population
Table 14.1.7	Summary of History of Atrial Fibrillation Safety Population
Table 14.1.8	Summary of Epicardial and Endocardial Lesions
Table 14.1.9	Summary of Convergent Procedure and Cardiac Ablation Procedure
Table 14.1.10	Summary of Rhythm Type during Procedure
Table 14.2.1.1	Analysis of AF/AFL/AT Freedom During Efficacy Evaluation Period (Primary Efficacy Analysis) ITT Population, Primary Imputation Method
Table 14.2.1.2	Analysis of AF/AFL/AT Freedom During Efficacy Evaluation Period mITT Population, Primary Imputation Method
Table 14.2.1.3	Analysis of AF/AFL/AT Freedom During Efficacy Evaluation Period PP Population
Table 14.2.1.4	Analysis of AF/AFL/AT Freedom During Efficacy Evaluation Period ITT Population, Multiple Imputation Method
Figure 14.2.1.5	Forest Plot of AF/AFL/AT Freedom During Efficacy Evaluation Period by Subgroups ITT Population, Primary Imputation Method
Figure 14.2.1.6.1	Tipping Point Plot of AF/AFL/AT Freedom During Efficacy Evaluation Period ITT Population
Figure 14.2.1.6.2	Tipping Point Plot of AF/AFL/AT Freedom During Efficacy Evaluation Period mITT Population
Table 14.2.1.7	Sequential Testing of Endpoints: Multiplicity Adjustment ITT Population

Table 14.2.2.1	Analysis of AF Burden (90% Reduction) ITT Population
Table 14.2.2.4	Analysis of AF Burden (90% Reduction) with Class I/III AAD Usage ITT Population
Table 14.2.2.5	Analysis of AF Burden (75% Reduction) ITT Population
Table 14.2.2.8	Analysis of AF Burden (75% Reduction) with Class I/III AAD Usage ITT Population
Table 14.2.2.9	Analysis of AF Burden (No More than 12% AF Burden) ITT Population
Table 14.2.2.12	Analysis of AF Burden (No More than 12% AF Burden) with Class I/III AAD Usage ITT Population
Table 14.2.3.1	Secondary Effectiveness Outcome Analysis - AF Freedom During Efficacy Evaluation Period ITT Population, Primary Imputation Method
Table 14.2.4.1	Analysis of SF-36 Health Component Scores and Transformed Scale Scores ITT Population
Table 14.2.5.1	Analysis of Atrial Fibrillation Severity Scale (AFSS) Scores ITT Population
Table 14.2.6.1	Analysis of Six Minute Walk Test Results ITT Population
Table 14.2.7.1	Analysis of Change in LVEF ITT Population
Table 14.2.8.1	Analysis of Change in Left Atrial Size ITT Population
Table 14.2.9	Analysis of Hospitalizations ITT Population
Table 14.2.10	Analysis of Rhythm Disturbance Treatments ITT Population
Table 14.2.11	Analysis of Long-Term Follow-Up ITT Population
Table 14.3.1.1	Summary of Major Adverse Events (MAEs) (Primary Safety Endpoint) Safety Population
Table 14.3.1.2	Summary of Treatment-Emergent Adverse Events Safety Population
Table 14.3.1.3	Summary of Treatment-Emergent Adverse Events with Onset through the 30th Day Post-Procedure Safety Population
Table 14.3.1.4	Summary of Treatment-Emergent Serious Adverse Events Safety Population
Table 14.3.1.5	Summary of Severe Treatment-Emergent Adverse Events Safety Population
Table 14.3.1.6	Summary of Treatment-Emergent Adverse Events Leading to Withdrawal from Study Safety Population
Table 14.3.1.7	Summary of Treatment-Emergent Adverse Events Related to Study Treatment/Procedure Safety Population
Table 14.3.1.8	Summary of Treatment-Emergent Adverse Events Related to Endocardial Catheter System Safety Population
Table 14.3.1.9	Summary of Treatment-Emergent Adverse Events Related to Study Device Safety Population
Table 14.3.1.10	Summary of Treatment-Emergent Adverse Events by Severity Safety Population

15.1.2 **Listings**

Listing 16.2.1.1	Subject Disposition
Listing 16.2.1.2	Informed Consent
Listing 16.2.1.3	Eligibility and Randomization
Listing 16.2.2	Protocol Violations and Deviations
Listing 16.2.3.1	Analysis Populations
Listing 16.2.3.2	Subject Visits
Listing 16.2.4.1	Demographic and Baseline Characteristics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Cardiac History
Listing 16.2.4.4	Cardiac Interventions
Listing 16.2.4.5	History of Atrial Fibrillation
Listing 16.2.4.6	Cardioversion History
Listing 16.2.4.7	Intra-Operative Evaluation
Listing 16.2.4.8	Epicardial Lesions (EPi-Sense-AF Treatment Arm)
Listing 16.2.4.9	Endocardial Lesions (EPi-Sense-AF Treatment Arm)
Listing 16.2.4.10	Endocardial Lesions (Catheter Ablation Treatment Arm)
Listing 16.2.4.11	Epicardial and Endocardial Procedure Data from Pre-Procedure Visit
Listing 16.2.4.12	Convergent Procedure Data (Epi-Sense-AF Treatment Arm)
Listing 16.2.4.13	Cardiac Ablation Procedure Data (Cardiac Ablation Treatment Arm)
Listing 16.2.4.14	ACT Data
Listing 16.2.4.15	Device Information (Epicardial)
Listing 16.2.4.16	Device Information (Endocardial)
Listing 16.2.4.17	Rhythm Type, Pre- and Post-Procedure
Listing 16.2.6.1	Freedom from AF, AFL, and AT During Efficacy Evaluation Period mITT Population
Listing 16.2.6.2	Freedom from Atrial Fibrillation (AF) During Efficacy Evaluation Period mITT Population
Listing 16.2.6.3	Holter Monitor Findings
Listing 16.2.6.4	Echocardiography
Listing 16.2.6.5	12-Lead Electrocardiogram
Listing 16.2.6.6	MRI/CT Scan Data
Listing 16.2.6.7	Rhythm Disturbance Evaluation
Listing 16.2.6.8	Six Minute Walk Test
Listing 16.2.6.9	SF-36 Item Results
Listing 16.2.6.10	SF-36 Health Component Scores and Standardized Scale Scores
Listing 16.2.6.11	Atrial Fibrillation Severity Scale (AFSS)
Listing 16.2.6.12	Individual Hospitalizations
Listing 16.2.6.13	Overview of Hospitalizations
Listing 16.2.7.1	Major Adverse Events
Listing 16.2.7.2	Potential MAEs Adjudicated as Non-Events

Listing 16.2.7.3	Adverse Events
Listing 16.2.7.4	Adverse Event Summaries
Listing 16.2.7.5	Serious Adverse Events
Listing 16.2.7.6	Adverse Events Leading to Withdrawal from Study
Listing 16.2.7.7	Adverse Events Leading to Death
Listing 16.2.7.8	Unanticipated Adverse Device Effects
Listing 16.2.7.9	Deaths
Listing 16.2.7.10	Non-Study Medications
Listing 16.2.7.11	Class I or III AAD Medications