TREATMENT OF PERSISTENT ATRIAL FIBRILLATION WITH THE SPHERE-9 MAPPING AND ABLATION CATHETER AND THE AFFERA MAPPING AND ABLATION SYSTEM

STATISTICAL ANALYSIS PLAN

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Clinical Investigation Plan	CP-00009
Investigational Device	Sphere-9™ Mapping and Ablation Catheter with the Affera Mapping and Ablation System
Description	Prospective, multicenter, randomized interventional study to evaluate the safety and effectiveness of the Sphere-9 Mapping and Ablation Catheter with the Affera Mapping and Ablation System for the treatment of symptomatic persistent atrial fibrillation (PerAF) refractory or intolerant to drugs using radiofrequency (RF) and pulsed field (PF) ablation
Sponsor and Investigational Device Manufacturer	Affera, Inc. 320 Nevada St, Suite 401 Newton, MA 02460 USA

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Revision History

Revision	Change Order	Description
C	CO-002554	Record of approval and change history is in the EDCS

1 ABBREVIATIONS

AAD	Antiarrhythmic Drug
AE	Adverse Event
AF	Atrial Fibrillation
CVA	Cerebrovascular Accident
MoCA	Montreal Cognitive Assessment
NIM	Non-Inferiority Margin
PerAF	Persistent Atrial Fibrillation
PF	Pulsed Field
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QOL	Quality of Life
RF	Radiofrequency
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCE	Silent Cerebral Event
SCL	Silent Cerebral Lesion
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiogram
TTM	Transtelephonic Monitoring

2 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to document the methods and rationale for the statistical analysis to be performed as part of clinical investigation plan CP-00009 (Treatment of Persistent Atrial Fibrillation with the Sphere-9 Mapping and Ablation Catheter and the Affera Mapping and Ablation System). This is a prospective, multicenter, randomized clinical evaluation of the Sphere-9 Mapping and Ablation Catheter with the Affera Mapping and Ablation System. Subjects are randomly assigned 1:1 to receive treatment with either the Sphere-9 Mapping and Ablation Catheter and the Affera Mapping and Ablation System (investigational device) or the THERMOCOOL SMARTTOUCH® SF Catheter (control device). Subjects are blinded to treatment assignment.

This SAP includes analysis to be performed for the corresponding Pre-Market Approval (PMA) submission and the study final report. Additional statistical analysis not described in this SAP may also be performed.

2.1 BACKGROUND

2.1.1 ATRIAL FIBRILLATION

Atrial fibrillation (AF) is a supraventricular tachycardia that manifests as a rapid, irregular atrial rhythm with no clearly defined P-wave on the electrocardiogram. AF that terminates within seven days is defined as paroxysmal, while AF lasting longer than seven days is defined as persistent. Long-standing persistent AF is defined as continuous AF persisting for longer than 12 months [1].

AF carries significant risks. AF leads to dramatically increased risk of stroke and mortality, particularly among patients with persistent forms of AF. Furthermore, AF is often symptomatic, leading to fatigue and reduced quality of life (QOL); however, it carries similar risks with or without symptoms [1].

2.1.2 DEMOGRAPHIC PROFILE OF ATRIAL FIBRILLATION PATIENTS

AF affects an estimated 37 million people worldwide [2]. The lifetime risk of developing AF after age 40 was 26% and 23% for men and women, respectively, in the Framingham Heart Study [3]. AF incidence rises rapidly with advancing age, and approximately one-fourth of adults diagnosed with AF are at least 80 years old [3, 4]. AF incidence is higher among whites than among African Americans [5].

Awareness of atrial fibrillation is poor [6], and disparities in awareness and treatment of AF have been identified. Factors identified as being associated with lack of awareness of AF have included race, lower education, rural location, lower number of general practitioner visits, and lower cognition [7, 8].

In the recent PRECEPT and STOP Persistent AF studies for catheter ablation to treat persistent AF (PerAF), the mean age was 65 years, with a standard deviation of 9 years. Approximately

70% of treated subjects in each study were male. Less than 10% of subjects treated in each study were non-white, and less than 2% were Black or African American [9, 10].

2.1.3 ABLATION OF ATRIAL FIBRILLATION

Thermal ablation using radiofrequency (RF) energy has become a widely accepted treatment for many tachyarrhythmias and is considered first-line therapy in some cases [11, 1]. The success rate of RF catheter ablation for treating atrial fibrillation has been found to be superior to that of antiarrhythmic drugs. For example, the RAAFT-2 trial found that catheter ablation led to a 55% recurrence rate for atrial fibrillation or atrial tachycardia at 2 years follow-up compared to 72% recurrence using antiarrhythmic drugs [1]. Similarly, recurrence of AF, atrial flutter, or atrial tachycardia in the CABANA trial favored catheter ablation over drug therapy with a hazard ratio of 0.53, and analysis based on treatment received suggests a benefit from ablation in terms of death and hospitalization [12].

Catheter ablation is considered a reasonable treatment (Class IIa) for the treatment of symptomatic persistent AF refractory or intolerant to antiarrhythmic drugs. Two ablation catheters have been approved for treatment of drug-refractory persistent AF: the THERMOCOOL SMARTTOUCH® SF Catheter, which is a focal RF ablation catheter; and the Arctic Front Advance™ Cardiac Cryoablation Catheter. Electrical isolation of all pulmonary veins (PVs) is recommended (Class I) as part of all AF ablation procedures. However, PV reconnection is common, and repeat ablation is often necessary [1, 13].

Catheter ablation of AF is often accomplished by delivering focal RF energy in a point-by-point fashion to create circles (e.g. to isolate PVs) and/or lines (e.g. to block an arrhythmogenic channel). RF energy delivery through an electrode at the tip of an ablation catheter causes resistive heating in tissue, which, along with conductive heating, leads to thermal ablation of cardiac tissue. Features such as saline irrigation and temperature feedback can help to avoid the formation of thrombus and char due to blood heating during RF delivery [1].

Pulsed field (PF) ablation, also known as irreversible electroporation, relies on the application of non-thermal electrical pulses to form pores in the cell membranes of target tissue resulting in tissue apoptosis or necrosis. Recently published preclinical and clinical research suggests that PF ablation may be as effective as RF ablation while reducing risks associated with RF ablation such as damage to collateral structures [14, 15, 16, 17].

In the recent PRECEPT pivotal IDE study of the THERMOCOOL SMARTTOUCH® SF catheter for treatment of persistent AF (NCT02817776), only PV isolation was required; linear ablation lines including left atrial roof line, mitral isthmus line, left atrial floor line, and cavotricuspid isthmus line were only required to treat documented macro-reentrant atrial tachycardias. Results of the PRECEPT study showed that a left atrial roof line was delivered in just under half (48.6%) of the per-protocol group, and a cavotricuspid isthmus line was delivered in just over one-third (35.2%) of the per protocol group. A left inferior PV mitral line and other linear lesions were each delivered in less than 10% of patients in the per-protocol group (7.8% and 8.9%, respectively) [9].

2.1.4 SAFETY OF AF ABLATION

A review of data from the Nationwide Inpatient Sample between 2000 and 2010 found an overall incidence of complications of 6.3%, with a trend of increasing complications over that period [18]. A 2010 questionnaire-based survey of centers performing catheter ablation for atrial fibrillation reported a major complication rate of 4.5% [19]. A 2017 analysis of prospective data from the ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry reported procedure-related complications in 7.8% [20]. In the recent PRECEPT pivotal IDE study of the THERMOCOOL SMARTTOUCH® SF catheter for treatment of persistent AF (NCT02817776), which used a similar primary safety endpoint to this protocol, the rate of the primary safety endpoint was 4.7% [21]. The PRECEPT study used an objective performance criterion (OPC) of 16%, based on an expected safety event rate of 8% and an 8% region of indifference, for analyzing the primary safety endpoint [22].

Pivotal IDE studies of focal catheter ablation for paroxysmal AF have also used similar primary safety endpoints. The DIAMOND-AF pivotal IDE study of the DiamondTemp ablation system for treatment of paroxysmal AF (NCT03334630) reported a primary safety event in 3.3% of subjects treated with the investigational device and in 6.6% of subjects treated with the control device (TactiCath™ Quartz) [23]. The SMART-SF study (NCT02359890), which evaluated the THERMOCOOL SMARTTOUCH® SF catheter for the treatment of paroxysmal AF, reported a primary adverse event in 2.6% of subjects (95% CI 0.7-6.5%). However, the SMART-SF study only evaluated early safety and acute effectiveness, so the chronic effectiveness of the treatments was not reported [24]. An OPC of 14% was used for analysis of the primary safety endpoint in SMART-SF [25]. The SMART-AF (NCT01385202) study was a pivotal IDE evaluating the THERMOCOOL SMARTTOUCH® catheter for treatment of paroxysmal AF, with primary safety and effectiveness endpoints similar to this protocol. The incidence of primary adverse events in SMART-AF was 9.9% (95% CI 5.8-15.6%) [26]. The OPC used for SMART-AF was not reported [27] but was presumably higher than the upper confidence bound of 15.6% based on the study's success.

2.1.5 CLINICAL OUTCOMES OF AF ABLATION

In a 2018 systematic literature review, single-procedure clinical success in treating persistent AF was estimated at 47% (95% CI 40-54%) across 18 cohorts between 2010 and 2015. Single-procedure clinical success in treating any AF with pulmonary vein isolation (PVI) plus linear ablation was estimated at 44% (95% CI 36-53%) across 10 cohorts over the same time period. Overall, this review found declining clinical success for AF ablation between 2001 and 2015 [28, 28]. The 2017 HRS consensus on AF ablation recommended a minimum acceptable success rate for treatment of persistent AF of 40% [1]. Subsequent single-arm pivotal IDE studies, including the PRECEPT study, used this minimum rate as an objective performance criterion for primary effectiveness. In the recent PRECEPT pivotal IDE study of the THERMOCOOL SMARTTOUCH® SF catheter for treatment of persistent AF (NCT02817776), primary effectiveness success was 59.3% through the end of the nine-month effectiveness evaluation period [21]. However, in contrast to this protocol, PRECEPT used a 6-month blanking and therapy consolidation period, and repeat ablation was allowed during that period (which occurred in 5.7%) [29].

3 STUDY OBJECTIVES

3.1 PRIMARY STUDY OBJECTIVES

The objectives of this study are to evaluate the safety and effectiveness of the Sphere-9 Mapping and Ablation Catheter with the Affera Mapping and Ablation System for the treatment of symptomatic persistent atrial fibrillation (PerAF) refractory or intolerant to drugs using radiofrequency (RF) and pulsed field (PF) ablation. This study aims to demonstrate safety and effectiveness non-inferiority compared to the control device.

4 STUDY ENDPOINTS

4.1 PRIMARY SAFETY ENDPOINT

The primary safety endpoint is the incidence of the following device- or procedure-related serious adverse events (SAEs) following the index ablation procedure:

Within 7 days:

- Death
- Myocardial infarction
- Phrenic nerve paralysis
- Transient ischemic attack (TIA)
- Stroke/cerebrovascular accident (CVA)
- Thromboembolism
- Major vascular access complications / bleeding
- Heart block
- Gastroparesis
- Severe pericarditis
- Hospitalization (initial and prolonged) due to cardiovascular or pulmonary AE‡

Within 30 days:

- Cardiac tamponade / perforation

Within 90 days:

- Atrio-esophageal fistula

Within 180 days:

- Pulmonary vein stenosis

‡ Excludes hospitalization due to AF/AFL/AT recurrence

An objective performance criterion (OPC) of 16% was used for the primary safety endpoint in the PRECEPT study of the THERMOCOOL SMARTTOUCH® SF catheter for treatment of persistent AF (NCT02817776) based on an expected rate of 8% with an 8% region of indifference [22]. The reported rate of the primary safety endpoint in that study was 4.7% [21]. Other recent studies of RF ablation for the treatment of AF (paroxysmal or persistent) have reported primary adverse event rates as high as 9.9% [26]. For this study, a non-inferiority margin (NIM) of 8% between the investigational group and the control group will be used for the primary analysis of the Primary Safety Endpoint.

4.2 PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint is freedom from documented recurrence of AF, atrial tachycardia (AT), or atrial flutter (AFL) based on electrocardiographic data through 12-month follow-up and excluding a 90-day blanking period. The following are considered primary effectiveness endpoint failures:

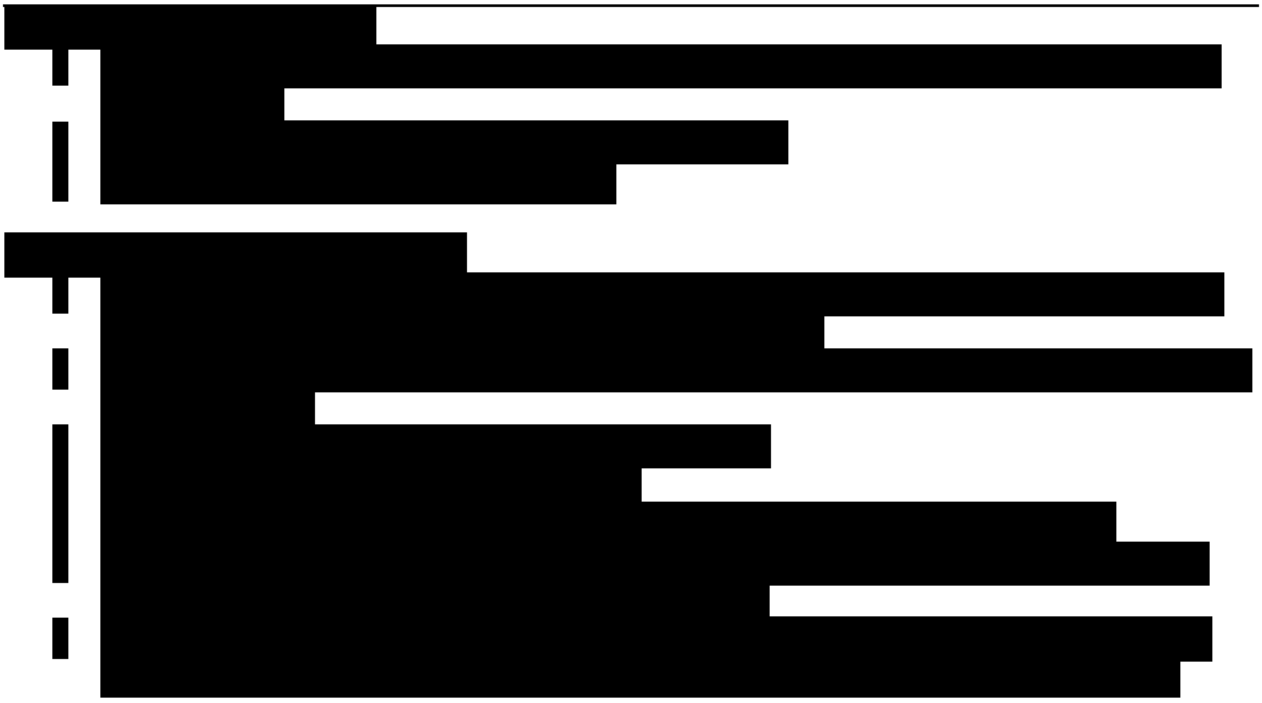
- Inability to isolate all targeted pulmonary veins during the index procedure.
- Ablation using devices other than the assigned study device for any left atrial ablation during the index procedure. (The assigned study device is the Sphere-9 Catheter for the investigational arm and the THERMOCOOL SMARTTOUCH SF for the control arm.)

- Any repeat ablation, surgical ablation, or arrhythmia surgery for treatment of recurrent AF/AT/AFL after the index procedure.
- Documented AF/AT/AFL recurrence after the 90-day blanking period.
- Class I or III AAD dose increase from the historic maximum ineffective dose (prior to the index procedure) or initiation of a new Class I or III AAD for treatment of AF/AT/AFL after the 90-day blanking period.
- DC cardioversion for AF/AT/AFL after the 90-day blanking period.

The blanking period is the first 90 days after the index ablation procedure. The effectiveness evaluation period will be from Day 91 through Day 360. AAD dose changes made at the Day 90 visit, within the follow-up window, will be considered to have occurred within the 90-day blanking period.

As discussed in Section 2.1.5, an objective performance criterion (OPC) of 40% was used for the primary effectiveness endpoint in the PRECEPT study of the THERMOCOOL SMARTTOUCH® SF catheter for treatment of persistent AF (NCT02817776) [22]. An OPC of 40% was proposed as the minimum chronic acceptable success rate in the 2017 HRS consensus but is somewhat conservative compared to the range of success rates reported in a more recent meta-analysis [1, 28]. The reported rate of the primary effectiveness endpoint in the PRECEPT study was 59.3%, nearly 20% greater than an OPC of 40% [21]. For this study, a non-inferiority margin (NIM) of 15% between the investigational group and the control group will be used for the primary analysis of the Primary Effectiveness Endpoint.

4.3 SECONDARY ENDPOINTS



Secondary Performance Endpoints:

[redacted]

- Procedure time, defined as the time from elapsed from first venous access to last sheath removal
- Treatment time, defined as the time from the start of the first ablation delivery to the end of the last ablation delivery
- Total energy application time during the ablation procedure

[redacted]

5 STATISTICAL METHODS

The objectives of this study are to evaluate the safety and effectiveness of the Sphere-9 Mapping and Ablation Catheter with the Affera Mapping and Ablation System for the treatment of symptomatic persistent atrial fibrillation (PerAF) refractory or intolerant to drugs using radiofrequency (RF) and pulsed field (PF) ablation. Subjects will be randomly assigned using a fixed 1:1 allocation to receive treatment with either the investigational device or the control device. Subjects will be blinded to treatment assignment. Randomization will be blocked and stratified by site and by enrollment in the Neurological Assessment Sub-Study.

5.1 GENERAL CONSIDERATIONS

Quantitative variables will be summarized using standard descriptive statistics: number of non-missing observations, mean, standard deviation, median, minimum, maximum, and 95% confidence interval (if appropriate). Number and percent of missing data, if any, will be summarized.

Categorical or semi-quantitative variables will be summarized using classical frequency statistics: number of non-missing observations, frequency, and percentage by category. Number and percent of missing data, if any, will be summarized. In analyzing variables involving a combination of events (e.g., Primary Effectiveness Failures, Primary Safety Events, specific types of adverse events), only one event per subject will be counted. Confidence intervals will be reported using the Wilson score interval (for individual variables) or the Farrington-Manning method (for difference between variables) as appropriate [30].

For survival function analysis, the Kaplan-Meier estimator will be used with the exponential Greenwood formula for confidence intervals. The log-rank test will be used for comparisons between treatment arms. Subjects without failure during the follow-up period will be censored at the date of last study contact recorded (e.g., last study visit, or study exit). In case of failure at the Day 360 visit, within the visit window but beyond study day 360, the date of failure will be set to study day 360 so that the failure is included in the survival analysis.

The study day is calculated as days since the index ablation procedure. The day of the index ablation procedure is study day 0. The blanking period extends from study day 0 through study day 90. The effectiveness evaluation period extends from study day 91 through study day 360.

Subject age will be reported as age at time of screening.

See Table 1 for subject cohort definitions.

Table 1. Subject cohorts for statistical analysis.

Intention to Treat (ITT) Cohort	Subjects who provide informed consent and are randomized.
Primary Analysis Cohort (PAC)	Subjects who provide informed consent, are randomized, and undergo insertion of the assigned study device (investigational or control), defined as the device emerging from the sheath into the bloodstream.
Roll-In Cohort	Subjects who provide informed consent, are assigned to Roll-In (not randomized), and undergo insertion of the investigational device, defined as the device emerging from the sheath into the bloodstream.
[redacted]	[redacted]

5.2 PRIMARY ANALYSES

This study aims to demonstrate non-inferiority of both safety and effectiveness of the investigational device compared to the control device. The non-inferiority margin (NIM) for evaluating Primary Safety is 8%. The NIM for evaluating Primary Effectiveness is 15%. The Primary Analyses will be conducted using the PAC (see Table 1).

The study will be declared a success if the null hypothesis for both the primary safety and primary effectiveness endpoints are successfully rejected.

Primary Safety Analysis

The null hypothesis (H_0) for the Primary Safety Analysis is that the true rate of primary safety events for the investigational device (Q_I) is equal to or greater than the true rate for the control device (Q_C) plus a NIM of 0.08. The alternative hypothesis (H_A) is that the rate of primary safety events for the investigational arm (Q_I) is less than the rate of primary safety events for the control arm (Q_C) plus the NIM of 0.08.

$$H_0: Q_I \geq Q_C + 0.08$$
$$H_A: Q_I < Q_C + 0.08$$

The Primary Safety Analysis will be performed at a one-sided Type I error rate of $\alpha = 0.05$. The Farrington-Manning method will be used to calculate the upper 95% confidence bound for the difference ($Q_I - Q_C$) between the rate of the Primary Safety Endpoint in the investigational arm (Q_I) and the rate of the Primary Safety Endpoint in the control arm (Q_C). If the upper confidence

bound is less than 0.08, the study will be considered to have demonstrated safety of the investigational device. The *p*-value for the Farrington-Manning test will be reported.

Primary Effectiveness Analysis

The null hypothesis (H_0) is that the true rate of Primary Effectiveness Endpoint success (no failures through Day 360) for the investigational device (P_I) is less than or equal to the true rate for the control device (P_C) minus the NIM of 0.15. The alternative hypothesis (H_A) is that the success rate for the investigational arm (P_I) is greater than the success rate for the control device (P_C) minus the NIM of 0.15.

H_0: $P_I \leq P_C - 0.15$
H_A: $P_I > P_C - 0.15$

The Primary Effectiveness Analysis will be performed at a one-sided Type I error rate of $\alpha = 0.025$. The Farrington-Manning method will be used to calculate the lower 97.5% confidence bound for the difference ($P_I - P_C$) between the rate of the Primary Effectiveness Endpoint in the investigational arm (P_I) and the rate of the Primary Effectiveness Endpoint in the control arm (P_C). If the lower confidence bound is greater than −0.15, the study will be considered to have demonstrated effectiveness of the investigational device. The *p*-value for the Farrington-Manning test will be reported.

If the Primary Effectiveness Endpoint rate is determined to be less than 40% for either the investigational arm or the control arm, the Primary Effectiveness analysis will be difficult to interpret, and additional analyses will be necessary to explain the poor device performance.

5.2.1 POOLABILITY ACROSS SITES

Data from different sites are expected to be poolable based on (i) consistent site selection criteria based on the Sponsor's standard operating procedures (SOPs), (ii) the use of a consistent clinical investigation plan with well-defined inclusion/exclusion criteria, and (iii) site monitoring to ensure compliance. To minimize the influence of any individual site, each site should not enroll more than 20% of the total enrollment.

A regression approach will be used to evaluate homogeneity of treatment effect (Primary Safety and Primary Effectiveness) across sites using the PAC. This will use a logistic regression model with fixed terms for randomized treatment group, site, and the interaction of treatment group and site. If necessary, Firth's adjustment will be used to handle sparse data. If heterogeneity across sites is found to be potentially significant ($p < 0.1$), additional analyses will be conducted to investigate sources of the apparent differences across sites. If data from different sites are not found to be poolable, a random-effects model will be fit to examine the impact of site heterogeneity on the primary endpoints.

5.2.2 SENSITIVITY ANALYSIS

Multiple imputation of the primary effectiveness endpoint will be employed to address missing data. This will be based on a fully conditional specification logistic regression approach with 100 imputed data sets. Imputation will be performed separately by treatment group. The imputation

model will include the following covariates: age, sex, and LA size. Covariates will be included in the model in the order listed above. Results of the imputation will be summarized with the confidence interval for the difference between treatment groups for the primary effectiveness endpoint, as well as the corresponding non-inferiority *p*-value.

Tipping point analyses will also be conducted where the hazard of failure for those with missing outcomes are increased (and decreased) to explore the impact of potential missing not at random on the primary effectiveness analysis.

Reasons for missing data within the follow-up period will be reported. Transtelephonic monitoring (TTM) compliance will be calculated for each subject in the PAC as the number of TTM recordings during a given period divided by the expected number of TTM recordings during that period. Expected transmissions will be estimated based on a 7-day week and a 31-day month.

5.2.3 SUBGROUP ANALYSES

Subgroup analyses will be performed to evaluate the primary safety and effectiveness endpoints within subgroups of subjects. Subgroup analysis will be based on at least the following demographic and baseline variables:

- Age (<65 years and ≥65 years)
- Sex
- LA size (<45mm and ≥45mm)

The primary endpoints will be assessed separately within each patient subgroup. Results for each subgroup will be summarized by the endpoint rate for each treatment group, difference between treatment groups, and the corresponding nominal 95% confidence intervals. A regression approach will be used to assess heterogeneity of the treatment effect by subgroup, by including terms for treatment group, subgroup, and the interaction of treatment and subgroup. A *p*-value less than 0.1 for the interaction term will indicate evidence of heterogeneity and trigger additional analyses to explore and quantify the interaction.

5.2.4 SAMPLE SIZE

A sample size of 350 evaluable subjects is planned for the PAC. Power calculations were performed using the Farrington-Manning method [30]. Results can be reproduced using `nBinomial` in the R package `gsDesign` as illustrated below [31].

The underlying rate of the Primary Effectiveness Endpoint is assumed to be 0.60 for both the investigational device and the control device for the purpose of sample size calculation. Assuming a one-sided Type I error rate of 0.025, a sample size of 175 subjects in each arm of the PAC provides 82.2% power to reject the null hypothesis and demonstrate that the Primary Effectiveness of the investigational device is non-inferior to that of the control device.

```
> nBinomial(p1 = 0.6, p2 = 0.6, alpha = 0.025, beta = 0.2,
+ delta0 = -0.15, sided = 1, outtype = 3, scale = "Difference", n = 350)
    n  n1  n2 alpha sided      beta     Power    sigma0    sigma1  p1  p2 delta0       p10       p20
1 350 175 175 0.025     1 0.1778555 0.8221445 0.9700864 0.9797959 0.6 0.6  -0.15 0.5204364 0.6704364
```

Figure 1. R code for Primary Effectiveness sample size calculation.

The underlying rate of the Primary Safety Endpoint is assumed to be 0.08 for both the investigational device and the control device for the purpose of sample size calculation. Assuming a one-sided Type I error rate of 0.05, a sample size of 175 subjects in each arm of the PAC provides 84.0% power to reject the null hypothesis and demonstrate that the true rate of the Primary Safety Endpoint for the investigational device is non-inferior to that of the control device.

```
> nBinomial(0.08, 0.08, alpha = 0.05, beta = 0.2,
+ delta0 = -0.08, sided = 1, outtype = 3, scale = "Difference", n = 350)
    n  n1  n2 alpha sided      beta     Power    sigma0    sigma1   p1   p2 delta0        p10       p20
1 350 175 175  0.05     1 0.1599471 0.8400529 0.5817939 0.5425864 0.08 0.08  -0.08 0.05530385 0.1353039
```

Figure 2. R code for Primary Safety sample size calculation.

To ensure that investigators have adequate experience with the investigational device, each site will be permitted to use the investigational device in up to two enrolled non-randomized subjects (Roll-In Cohort). Subjects in the Roll-In Cohort will be analyzed separately from the PAC.

It is estimated that the attrition rate will be approximately 15%, leading to a planned randomized total of 410 subjects. The maximum number of Roll-In subjects will be 70. As a result, an overall maximum of 480 subjects will be enrolled in the study.

5.3 SECONDARY ANALYSES

If the Primary Analysis demonstrates safety and effectiveness of the investigational device (study success), Secondary Analyses will be performed to test the following secondary hypotheses using the PAC:

1. Total Energy Application Time Superiority: The null hypothesis ($H_0^{(1)}$) is that the mean total energy application time during the ablation procedure for the investigational device (μ_{ETI}) is greater than or equal to the mean time for the control device (μ_{ETC}). The alternative hypothesis ($H_A^{(1)}$) is that the mean total energy application time for the investigational device is less.

$$H_0^{(1)}: \mu_{\text{ETI}} \geq \mu_{\text{ETC}}$$
$$H_A^{(1)}: \mu_{\text{ETI}} < \mu_{\text{ETC}}$$

2. Treatment Time Superiority: The null hypothesis ($H_0^{(2)}$) is that the mean treatment time for the investigational device (μ_{TTI}) is greater than or equal to the mean treatment time for

the control device (μ_{TTC}). The alternative hypothesis ($H_{\mathrm{A}}^{(2)}$) is that the mean treatment time for the investigational device is less.

$$H_0^{(2)}: \mu_{\mathrm{TTI}} \geq \mu_{\mathrm{TTC}}$$
$$H_{\mathrm{A}}^{(2)}: \mu_{\mathrm{TTI}} < \mu_{\mathrm{TTC}}$$

3. Procedure Time Superiority: The null hypothesis ($H_0^{(3)}$) is that the mean procedure time for the investigational device (μ_{PTI}) is greater than or equal to the mean procedure time for the control device (μ_{PTC}). The alternative hypothesis ($H_{\mathrm{A}}^{(3)}$) is that the mean procedure time for the investigational device is less.

$$H_0^{(3)}: \mu_{\mathrm{PTI}} \geq \mu_{\mathrm{PTC}}$$
$$H_{\mathrm{A}}^{(3)}: \mu_{\mathrm{PTI}} < \mu_{\mathrm{PTC}}$$

4. Primary Effectiveness Superiority: The null hypothesis ($H_0^{(4)}$) is that the true rate of the Primary Effectiveness Endpoint for the investigational device (P_{I}) is less than or equal to the true rate for the control device (P_{C}). The alternative hypothesis ($H_{\mathrm{A}}^{(4)}$) is that the rate for the investigational device is greater.

$$H_0^{(4)}: P_{\mathrm{I}} \leq P_{\mathrm{C}}$$
$$H_{\mathrm{A}}^{(4)}: P_{\mathrm{I}} > P_{\mathrm{C}}$$

Sequential gate-keeping will be used to maintain a one-sided Type I error rate $\alpha \leq 0.025$. The secondary hypotheses above will only be tested if the Primary Analysis is successful (i.e., both safety and effectiveness of the investigational device have been demonstrated). Testing of the secondary hypotheses will proceed sequentially in the order listed above. The α level for each hypothesis test will be determined based on the "fallback" method of Wiens [32, 33] as follows:

1. $H_0^{(1)}$ will be tested at $\alpha_1 = \alpha_1' = 0.005$.
2. $H_0^{(2)}$ will only be tested if $H_0^{(1)}$ was rejected. In that case, $H_0^{(2)}$ will be tested at the same α level used for testing the previous hypothesis ($\alpha_2 = \alpha_1 = 0.005$).
3. $H_0^{(3)}$ will only be tested if *both* $H_0^{(1)}$ and $H_0^{(2)}$ were tested and rejected. In that case, $H_0^{(3)}$ will be tested at the same α level used for testing both previous hypotheses ($\alpha_3 = \alpha_2 = 0.005$).
4. $H_0^{(4)}$ will be tested regardless of the outcome of the preceding hypothesis tests. The α level for testing $H_0^{(4)}$ will be chosen as follows:
   a. If *any* of $H_0^{(1)}$, $H_0^{(2)}$, or $H_0^{(3)}$ was not rejected (i.e., failed), $H_0^{(4)}$ will be tested at $\alpha_4 = \alpha_4' = 0.020$.
   b. However, if *all* of $H_0^{(1)}$, $H_0^{(2)}$, and $H_0^{(3)}$ were tested and rejected (i.e., succeeded), $H_0^{(4)}$ will be tested at $\alpha_4 = \alpha_4' + \alpha_3 = 0.020 + 0.005 = 0.025$.

Any other *p*-values presented will be nominal, without adjustment for multiple comparisons.

5.4 Additional Analyses

No formal statistical hypothesis will be formulated for any additional analyses. Inferential statistics for these analyses will not be included in the device label.

Demographic and baseline characteristics of subjects in each analysis cohort will be reported, including but not limited to age, gender, race, ethnicity, baseline medications (including AADs and anticoagulation), medical history (including CHA_2DS_2-VASc and NYHA), arrhythmia history, height, weight, body mass index (BMI), and TTE measurements (including left atrial diameter).

Additional analyses for the primary endpoints will be performed using the PAC. The 95% confidence interval will be reported for the rate of the Primary Effectiveness Endpoint for both the investigational arm and the control arm, as well as the 95% confidence interval for the difference in rates between the two arms. Kaplan-Meier analysis and log-rank test will be performed.

[redacted]

The 90% confidence interval will be reported for the rate of the Primary Safety Endpoint for the both the investigational arm and the control arm, as well as the 90% confidence interval for the difference in rates between the two arms.

[redacted]

[redacted]

Secondary Performance Endpoints will be evaluated for both the investigational and control arm using the PAC.

[redacted]

For each of the following secondary performance endpoints, descriptive statistics will be reported as well as the 95% confidence interval for the difference between the investigational and control arm:

[redacted]

- Procedure time
- Treatment time
- Total energy application time during the ablation procedure

[redacted]

[redacted]

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