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Sustained Treatment of Paroxysmal Atrial Fibrillation Post-Approval Study (STOP AF PAS)

Statistical Analysis Plan

Version 2
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1 PURPOSE

This Statistical Analysis Plan (SAP) has been designed to document the rationale for the study design, and the planned analyses that will be included in study reports.

2 RATIONALE FOR STUDY DESIGN

2.1 Study Purpose

The pivotal trial (STOP-AF) of the Arctic Front® Cardiac Cryoablation Catheter System with the adjunctive use of the Freezor® MAX Cardiac Cryoablation Catheter to electrically isolate pulmonary veins (PV) in patients with paroxysmal atrial fibrillation (PAF), compared to a randomized drug control group has been performed and a final report submitted to the FDA resulting in product approval December 2010. A Continued Access Protocol trial (CAP-AF) was also conducted to allow collection of additional safety data following modifications implemented into the Arctic Front® Catheter and Cryoablation System. As part of the continued clinical development of the Arctic Front® Cardiac Cryoablation Catheter System, this Post-Approval Study (PAS) is being conducted to provide long-term safety and effectiveness monitoring/data, per the Pre-Market Approval order (P100010) by the Food and Drug Administration (FDA).

This PAS is a prospective multicenter, non-randomized, single arm, controlled, unblinded clinical study of up to 400 enrolled subjects with PAF who have failed one or more Atrial Fibrillation Drugs (AFDs). All study subjects will be receiving cryoablation with the study devices and, optionally (post-procedure), an Atrial Fibrillation Drug.

2.2 Study Scope

The study is expected to enroll subjects over an 18 - 24 month period with post procedural follow-up consisting of clinic visits at 3, 6 and 12 months, and 2 and 3 years. There was a CIP change in June of 2016 that reduced the follow-up time of this study from 5 years to 3 years. Prior to sites' activation of version 6 of the CIP, some subjects may also have been seen at 4-year or 5-year visits. This data will be included in the summary of safety outcomes.

Since the primary endpoint of the study is assessed at 3 years, the power of the study is not affected by this change.

More than 30 investigational sites in the United States and Canada have participated in this investigation. The Principal Investigator is Dr. Bradley Knight at Northwestern Memorial Hospital in Chicago, Illinois.

2.3 System Description

The investigational devices to be used in this trial are formally defined in the STOP AF PAS CIP version 6 (30JUN2016) Section 3. These devices include:

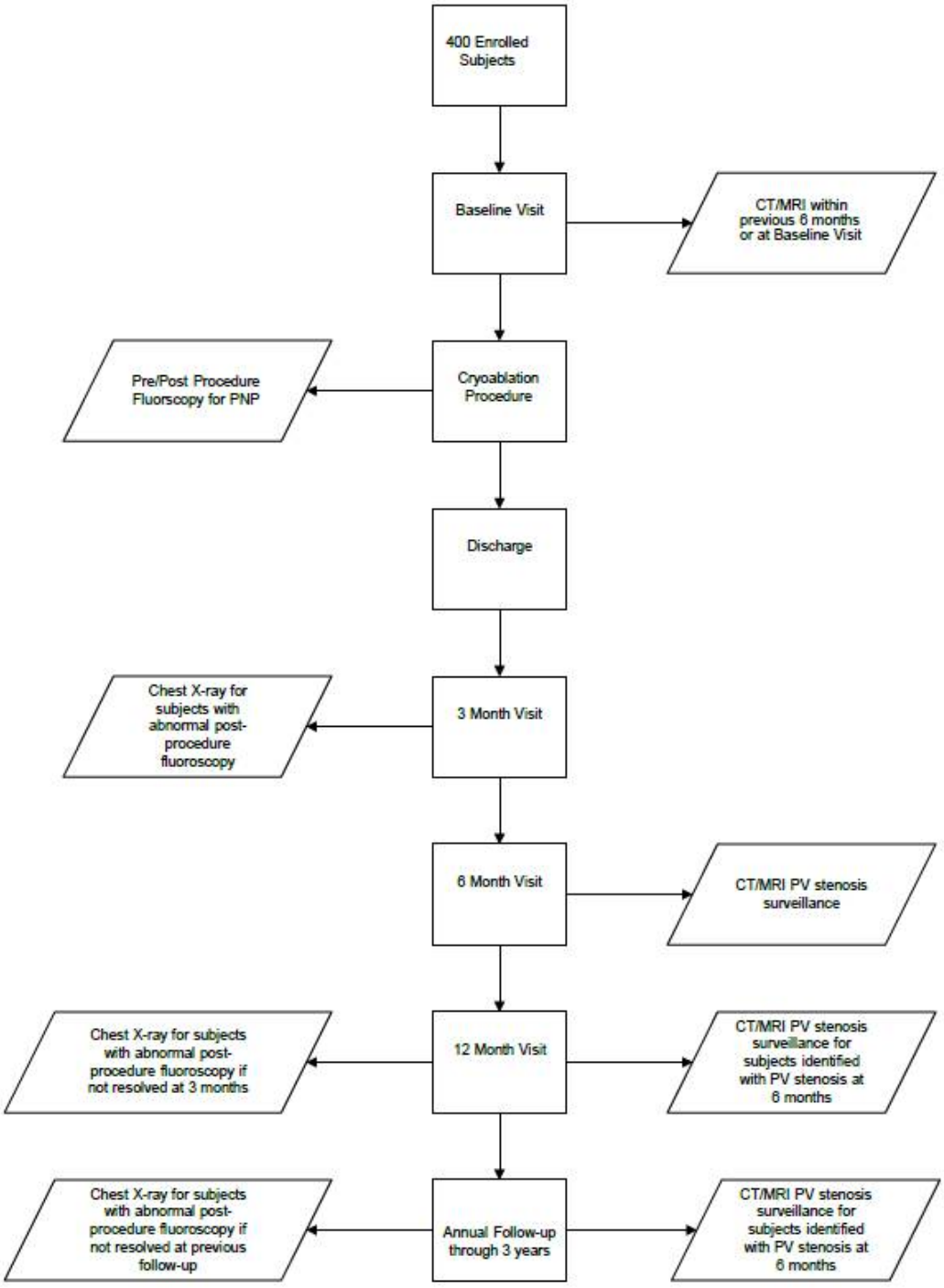
Arctic Front® Cardiac CryoAblation System, consisting of:

- Arctic Front® Cardiac CryoAblation Catheter OR
- Arctic Front Advance™ Cardiac CryoAblation Catheter
- Manual Retraction Kit
- The Freezor® MAX Cardiac CryoAblation Catheter
- Medtronic CryoCath CryoConsole

2.4 Data Collection

Clinical data are required to be collected at baseline/enrollment, procedure, post procedure, discharge, month (3, 6) follow-up, and year (1, 2, 3) follow-up. If a subject exits early, then a termination visit will also be conducted. The overall study design is summarized in Figure 1.

Figure 1: STOP AF PAS Overall Study Design



This SAP is based on Version6 of the STOP AF PAS Clinical Investigation Plan (30JUN2016).

3 DESCRIPTION OF ANALYSIS

3.1 General Summaries

3.1.1 Analysis Sets

Enrolled Set: any subjects who have a signed informed consent.

Intent-To-Treat Set (ITT): any enrolled subjects who meet all inclusion and exclusion criteria.

mITT (modified intent-to-treat) Set: any subjects within the ITT set with an Arctic Front® Cardiac CryoAblation Catheter System inserted into the vasculature for the purpose of this study.

All Treated Set: any subjects who have signed informed consent and have an Arctic Front® Cardiac CryoAblation Catheter System inserted into the vasculature.

3.1.2 Use of Adjudicated Data

For endpoint events that are to be adjudicated, only data fully adjudicated by the Adverse Event Adjudication Committee (AEAC) will be used in summaries and analyses. AEAC determination of Chronic Treatment Failure (CTF), Cryoablation Procedure Events (CPE), and Major Atrial Fibrillation Event (MAFE), and their respective onset dates, are what the endpoint analyses utilizing these events will be based on. For adverse events (AE) reporting, AEAC determination of seriousness, and relatedness status will be used. Note that for data freezes and analyses before the final report, it may not be possible for all data used to be adjudicated.

3.1.3 Description of Baseline Variables

The following baseline, disposition and procedural parameters reported on the case report forms (CRF) will be analyzed descriptively.

- The baseline and demographic characteristics, including but not limited to age, gender, race, height, weight, body mass index, relevant medical history, arrhythmic symptoms, comorbid conditions, cardiovascular medical history, and concomitant medications. The baseline demographic tables will be reported for both the Intent-To-Treat (ITT) Set and Modified Intent-To-Treat (mITT) Set.

- Subject disposition (analysis set allocation, discontinued along with primary reason for discontinuation, etc.) will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided.

- A summary of Cryoablation procedure information including Cryoablation parameters (number, duration, average temperature, etc.),cryocatheter insertion time, PV ablation time, and total fluoroscopy time will be summarized based on the modified intent-to-treat (mITT) set

Tables and descriptive statistics will be used to summarize subject data with respect to these variables. For quantitative variables, number of non-missing observations, mean, median, minimum, maximum and standard deviation will be calculated. For qualitative variables, percentages and counts will be calculated.

3.1.4 Special Considerations

3.1.4.1 Pooling of Study Centers for Analysis

A study center is defined as a treatment administration site or group of treatment administrative sites under the control and supervision of the same Principal Investigator. Each study center will be limited to enrolling no more than 50 subjects into the mITT set. Each center will be encouraged to enroll at least 10 subjects into the mITT set. This will prevent any single center from contributing a significant proportion of the subjects to the study. While every effort will be made to acquire similar enrollment from all participating centers, it is likely that some centers may enroll small numbers of subjects. Therefore (for assessment of heterogeneity only) the centers that contribute five or fewer subjects to the mITT dataset will be pooled into a single 'super center'. The participating centers with more than five subjects in the mITT dataset will be reported individually.

Assessments of heterogeneity will be performed for the primary effectiveness and safety objectives across the investigational study centers. Analysis of heterogeneity in primary endpoints will be conducted only in the final report.

The level of heterogeneity of pre-specified primary endpoints will be conducted using a random-effects meta-analytic approach. The R statistical software platform will be used to evaluate whether sites exhibit significant heterogeneity in event rates. If a Cochran's Q test for heterogeneity shows $p<0.15$, it will be taken as evidence of heterogeneity between sites. Evidence of between-site heterogeneity will not preclude pooling data; rather, it may result in further investigation into the sources of the apparent differences in event rates between sites. In addition, a graphical display (such as a forest plot) of the proportions of primary effectiveness events and primary safety events along with 95% confidence intervals for each center may be constructed.

3.1.4.2 Missing Data

The impact of missing data on the analysis of primary effectiveness and safety objectives is expected to be small since the Kaplan-Meier method will be performed for the primary objectives. For subjects who are lost to follow-up, the time to event will be censored at the last contact date.

Analysis will be based on available cases. The reasons for study withdrawal will be documented. There are no plans for imputation of any missing data. However, we will compare differences in baseline characteristics between subjects with complete data and subjects with early exit. Also, if the primary objectives are met ($p < 0.05$) at 3 years, with >

5 subjects exiting prior to the 3-year follow-up, a tipping point analysis will be conducted to assess sensitivity to missing data. Missing data is defined here as subjects with less than 3 years of follow-up.

Data will be sorted by ascending event times, and subjects who are censored prior to the 3-year visit are assigned an event time equal to a (date of last contact–index ablation date). Then, for each observation:

1) If the observation is censored, set time = time + 1 and event = 1.
2) Apply the log-rank test (specified in section 3.2.1 or 3.2.2 for efficacy and safety, respectively) to find the new two-sided p-value and 95% log-log confidence interval.

The first observation where the confidence interval includes the performance goal (and the corresponding p-value ≥ 0.05) is the tipping point for the primary safety analysis. For either primary endpoint, if fewer than 5 subjects have missing data, a worst-case analysis will be done instead of a tipping point analysis. This analysis will be performed in the mITT dataset.

3.1.5 Reports for which this Statistical Analysis Plan applies

This analysis plan applies to the study final report, and the analysis results may be reported in study-related publications and interim progress reports. Statistical analysis for study-related publications will not be limited to those defined in this plan.

3.2 Primary Objectives

The study will be considered a success if both primary effectiveness and safety objectives are met at one-sided 0.025 level of significance in the final analysis. The analysis will be conducted using all mITT subjects.

3.2.1 Primary Objective #1 (Primary Effectiveness Objective)

The primary effectiveness endpoint is the rate of subjects free of chronic treatment failure (CTF) at 36 Months.

3.2.1.1 Hypothesis

The following hypothesis will be tested in a one-sided test at the 0.025 significance level.
Ho: Pe ≤ 45%
Ha: Pe > 45%
where Pe is the probability of freedom from CTF at 36 months and 45% is the pre-specified performance goal based on the lower bound of 95% CI for the primary effectiveness rate in the STOP AF study.

3.2.1.2 Endpoint Definition

Chronic Treatment Failure is defined as:

- Documented atrial fibrillation lasting longer than 30 seconds (outside the 90 day blanking period) OR

- Intervention for atrial fibrillation (except for repeat cryoablation during the 90 day blanking period)

Intervention for atrial fibrillation is defined as: An invasive procedure intended for the definitive treatment of AF, including any ablation of the PVs or atrial triggers (other than protocol-specified ablation), interruption of AV nodal function, procedures to alter left atrial conduction or function such as the Maze procedure, or the implantation of an atrial pacemaker or atrial defibrillator; whether approved by relevant regulatory authorities or not for such indications; excluding electrical or pharmacologic cardioversion of arrhythmias and excluding procedures solely directed at the treatment of atrial flutter or atrial tachycardias. A reablation permitted under Section 5.12 of the protocol is not an AF intervention.

3.2.1.3 Analysis Methods

A. Statistical Methodology

The Kaplan-Meier method will be used to estimate the probability of chronic treatment success at 36 months follow-up. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed. The Kaplan-Meier estimate and its 95% log-log confidence interval will be constructed from the day of protocol specified ablation procedure (Day 0) through the end of follow-up. For subjects with a treatment failure, the days of follow-up will be computed as the days from Day 0 to the failure date. For subjects without failure events, days of follow-up will be computed as the days from Day 0 through the last follow-up. For subjects who are lost to follow-up, the last contact date will be used as the last follow-up date.

The survival curve will be presented through 36 months. Note that the phrases 'at 36 months' and 'through 36 months as used throughout includes events from the 3 year visit, even when it occurs more than 3 x 365 = 1,095 days from the start date. The 36 month visit may occur after 1,095 days since the visit window runs until 30 days past day 1,095. Rhythm monitoring that was initiated at the 36 month visit will be included in the analysis of the 36 month endpoint provided that the date of the documentation is no later than 30 days after the 36 month visit. Therefore, depending on the date of the 3 year visit, it is possible to include documentation as late as day 1,155. Not including such events after day 1,095 could underestimate the proportion at 3 years due to 36 month visits that occur after 1,095 days. This potential bias is addressed in the statistical analysis by considering the date of recurrence to be exactly 36 months from the study ablation procedure so that these events will be counted as CTF in the 36 month Kaplan-Meier analysis.

B. Determination of Subjects/Data for Analysis

The analysis will be conducted using the modified intent-to-treat (mITT) set.

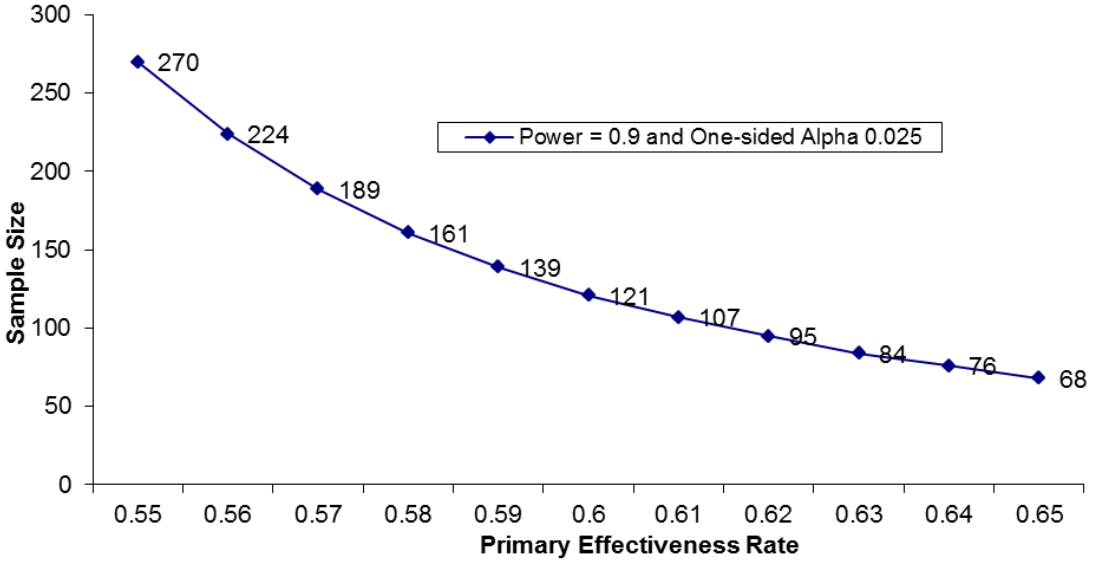
3.2.1.4 Sample Size Methods and Assumptions

Sample size was estimated using SAS v9.2 Proc Power. The sample size was calculated under an asymptotic z-test for a single binomial proportion with continuity adjustment under the following assumptions:
Power = 90%, Significance level = 0.025 (one-sided), Assumed underlying effectiveness rate = 55%, Performance goal = 45%.

Long-term (> 12 months) effectiveness of pulmonary vein isolation for the treatment of atrial fibrillation (AF) ranges from 44-70%, with 40% reported as the minimum goal by physicians[1]. Shah et al reported that the annual rate of atrial fibrillation recurrence after one year was 8.8% and Tzou et al reported a similar annual rate of 7%[2,3]. Based on the STOP AF results and assuming an annual rate of atrial fibrillation recurrence of 7-9%, the estimated effectiveness rate at 36 months would be approximately 55%. The performance goal of 45% was determined from the lower bound of 95% CI for the primary effectiveness rate in STOP AF study.

Figure 2 presents the sample size at different primary effectiveness rates under the assumptions outlined above.

Figure 2. Sample Size vs. Primary Effectiveness Rate



If the underlying effectiveness rate is assumed 55%, a total of 270 evaluable subjects will be required to provide 90% power to meet this effectiveness objective.

3.2.2 Primary Objective #2 (Primary Safety Objective)

The primary safety endpoint is the rate of subjects experiencing one or more Cryoablation Procedure Events (CPE) through 12 months.

3.2.2.1 Hypothesis

If the upper bound of the confidence interval for CPE rate at 12 months is less than the performance goal of 14.8%, we can conclude the primary safety objective is met.

The following hypothesis will be tested in a one-sided test at the 0.025 significance level.:

Ho: Ps ≥ 14.8%
Ha: Ps < 14.8%
where Ps is the probability of subjects with one or more CPEs and 14.8% is the pre specified performance goal based on the upper bound of 95% CI for the primary safety rate in the STOP AF study.

3.2.2.2 Endpoint Definition

A CPE is a device-related or procedure-related serious adverse event (SAE) with onset between the time of the subject's entry into the procedure room for the study-specified cryoablation procedure (Day 0) through the indicated onset intervals as set out in the following Table 1:

Table 1: Cryoablation Procedure Events

Cryoablation Procedure Events (CPEs)	Onset Interval
Access site complications requiring: Transfusion of 3 or more units or Surgical intervention or Permanent loss or functional impairment	Through 7 days
Cardiac damage (including MI) except for	Through 7 days
Pulmonary vein stenosis*	Through 12-months
Atrio-esophogeal fistula	Through 12-months
Embolic complications (including stroke)	Through 7 days
Arrhythmias	Through 7 days
Persistent phrenic nerve palsy**	Through 12-months
Death	Through 7 days

* CPE will be assessed at the completion of the follow-up visit, as determined by CT/MRI Core Lab.
** CPE will be assessed at the completion of the follow-up as determined by chest X-ray (insp/exp)

- Pulmonary vein stenosis is defined as > 75% reduction in the baseline area after 6-month follow-up.
- Phrenic nerve palsy (alternatively, Phrenic Nerve Injury or PNI) is defined as abnormal diaphragm excursion as demonstrated during the post-cryoablation procedure fluoroscopy. PNI events are considered persistent if they are unresolved at 12 months.

CPEs exclude

1. Adverse events that are normal and expected concomitants of catheterization and diagnostic and ablation electrophysiology (EP) procedures, such as induced arrhythmia and groin ecchymosis, but only IF that AE resolves completely AND involves only routine responses such as medication, fluids, compression, temporary pacing, or cardioversion.
2. Atrial fibrillation or atrial flutter occurring during post-procedural hospitalization.

- CPEs will be accrued for Retreated Subjects for the comparable 7 day period following a repeat cryoablation.

3.2.2.3 Analysis Methods

A. Statistical Methodology

The Kaplan-Meier method will be used to estimate the probability of a subject experiencing one or more CPE at 12 months follow-up. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed. The Kaplan-Meier estimate and its 95% log-log confidence interval will be constructed from the day of study specified cryoablation procedure (Day 0) through the end of follow-up. For subjects with safety events, the days of follow-up will be computed as the days from Day 0 to the onset date of the first safety event. For subjects without safety events, days of follow-up will be computed as the days from Day 0 through the last follow-up. For subjects who are lost to follow-up, the last contact date will be used as the last follow-up date.

The 12 month visit may occur after 365 days since the visit window runs until 30 days past day 365. Not including events that result from assessment at a 12-month visit, but after day 365 could underestimate the proportion at 1 year due to 12 month visits that occur after 365 days. This potential bias is addressed in the statistical analysis by considering the date of recurrence to be exactly 12 months (365 days) from the study ablation procedure so that these events will be counted as CPE in the 12-month Kaplan-Meier analysis.

B. Determination of Subjects/Data for Analysis

The analysis will be conducted using the modified intent-to-treat (mITT) set.

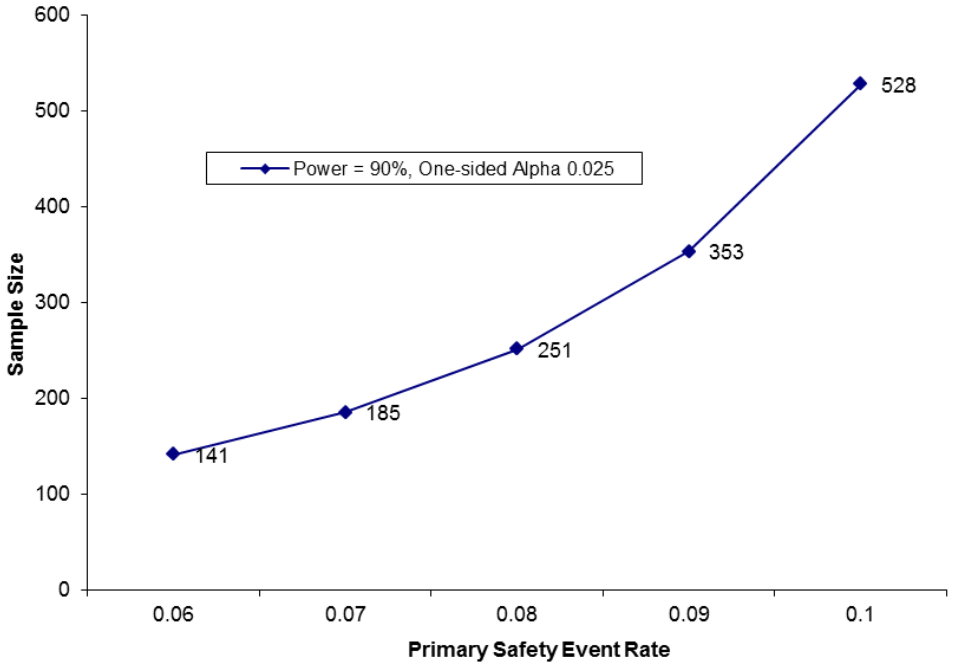
3.2.2.4 Sample Size Methods and Assumptions

Sample size was estimated using SAS v9.2 Proc Power. The sample size was calculated under an asymptotic z-test for a single binomial proportion with a continuity adjustment under the following assumptions:
Power = 90%, Significance level = 0.025 (one-sided), Assumed underlying primary safety event rate = 6%, Performance goal = 14.8%.

The performance goal of 14.8% is selected based on the same assumption defined in version 1.7 of the STOP AF Clinical Investigation plan (January 15, 2008):
"Based on a review of SSEDs for similar types of ablation trials, the expected rate for CPEs in a well-monitored trial of left atrial RF ablation for AF was estimated to be 10% (corresponding to a CPE-free rate of 90%). If 16 of 160 subjects were observed to have at least one CPEs then the resulting one-sided 95% upper confidence bound would be 14.8%."; where SSED is an abbreviation for Summary of Safety and Effectiveness Data.

Figure 3 presents the sample size at different primary safety event rates under the assumptions outlined above.

Figure 3. Sample Size vs. Primary Safety Event Rate



If the underlying safety event rate is assumed 6%, a total of 141 evaluable/mITT subjects will be required to provide 90% power to meet this safety objective.

3.3 Secondary Objectives

All secondary analyses will be exploratory and no formal hypotheses tested.

3.3.1 Secondary Objective #1 (Effectiveness Objective)

The probability of subjects free of chronic treatment failure at the 1 and 2 year follow-up visits will be estimated.

3.3.1.1 Hypothesis

There is no hypothesis.

3.3.1.2 Endpoint Definition

Chronic treatment failure is defined in Primary Objective #1, section 3.2.1.2. Subjects free of chronic treatment failure are those that do not meet that definition.

3.3.1.3 Analysis Methods

A. Statistical Methodology

The Kaplan-Meier method will be used to estimate the probability of chronic treatment success at 1 and 2 year follow-ups. The standard error will be approximated using Greenwood's formula. Two-sided 95% log-log confidence intervals for the probability will be constructed for each of the four follow-ups. The Kaplan-Meier estimates and their 95% log-log confidence intervals will be constructed from the day of protocol specified ablation procedure (Day 0) through the end of follow-up. For subjects with a treatment failure, the days of follow-up will be computed as the days from Day 0 to the failure date. For subjects without failure events, days of follow-up will be computed as the days from Day 0 through the last follow-up. For subjects who are lost to follow-up, the last contact date will be used as the last follow-up date.

B. Determination of Subjects/Data for Analysis

The estimations will be conducted using the modified intent-to-treat (mITT) set.

3.3.2 Secondary Objective #2 (Major Atrial Fibrillation Events)

The probability of subjects free of Major Atrial Fibrillation Events (MAFE) at the 1, 2, and 3 year follow-up visits will be estimated.

3.3.2.1 Hypothesis

There is no hypothesis.

3.3.2.2 Endpoint Definition

Major Atrial Fibrillation Event (MAFE): A MAFE is a serious adverse event (SAE) which has not been categorized as a CPE as set out in the following table:

Table 2: Major Atrial Fibrillation Events

Major Atrial Fibrillation Events (MAFEs):
Cardiovascular deaths
Hospitalizations for (primary reason): AF recurrence or ablation Atrial flutter ablation (excluding Type I) Systemic embolization (not stroke) Congestive heart failure Hemorrhagic event (not stroke) Antiarrhythmic drug: initiation, adjustment or complication
Myocardial infarction (MI)
Stroke

3.3.2.3 Analysis Methods

A. Statistical Methodology

The Kaplan-Meier method will be used to estimate the probability of a subject being free of MAFE at 1, 2, and 3 year follow-ups. The standard error will be approximated using Greenwood's formula. Two-sided 95% log-log confidence intervals for the probability will be constructed for each of the five follow-ups. The Kaplan-Meier estimates and their 95% log-log confidence intervals will be constructed from the day of study specified cryoablation procedure (Day 0) through the end of each follow-up. For subjects with a MAFE, time until an event will be computed as the number of days from Day 0 to the onset date of the first MAFE. For subjects without a MAFE, the number of days at-risk will be computed as the days from Day 0 through the last time they had an opportunity to report a MAFE, which includes scheduled study follow-up visits and their associated testing plus the termination visit, if done. For subjects who are "lost to follow-up", time from Day 0 until last contact date will be used as the number of days at-risk.

B. Determination of Subjects/Data for Analysis

The estimations will be conducted using the modified intent-to-treat (mITT) set.

3.3.3 Secondary Objective #3 (Long Term Safety Outcomes)

Device and procedure related events, serious adverse events (SAE), and other safety categories will be collected through the 3 year follow-up and reported descriptively.

3.3.3.1 Hypothesis

There is no hypothesis.

3.3.3.2 Endpoint Definition

Device and procedure related events, and SAEs are defined in section 7.2.1 of CIP version 6.

3.3.3.3 Analysis Methods

A. Statistical Methodology

For each event, the total number of events, the number of subjects with at least one event, and the percentage of subjects with at least one event will be reported. Totals and sub-totals will be reported in the same manner. All of these events will be categorized using the MedDRA or similar system, tabulated and listed in decreasing frequency order.

B. Determination of Subjects/Data for Analysis

The population(s) used for descriptive summarization will be the mITT set.

3.3.4 Secondary Objective #4 (Cryoablation)

Cryoablation procedure parameters will be summarized

3.3.4.1 Hypothesis

There is no hypothesis.

3.3.4.2 Endpoint Definition

- Cryoablation procedure parameters such as total number of cryoablation attempts, mean number of cryoablation attempts per attempted subject and number of successful cryoablations per subject will be summarized using descriptive statistics.
- Cryoablation temperature and ablation procedure time (duration) will be summarized using descriptive statistics.

3.3.4.3 Analysis Methods

A. Statistical Methodology

Tables and descriptive statistics will be used to summarize subject data with respect to these variables. For quantitative variables, number of non-missing observations, mean, median, minimum, maximum and standard deviation will be calculated. For qualitative variables, percentages and counts will be calculated. Summaries for index ablation and re-treatment procedures will be reported separately. Categories of 'other' will be reported in associated listings.

For the final report, most of the statistics reported will describe subject-level phenomena, requiring aggregation (for example, by taking the average, minimum or maximum) when measurements such as cryoablation temperature are recorded in the data at the ablation or application level.

B. Determination of Subjects/Data for Analysis

The population used for descriptive statistics will be the mITT set.

3.3.5 Secondary Objective #5 (Procedure and Fluoroscopy Time)

Total procedure time and total fluoroscopy time will be summarized.

3.3.5.1 Hypothesis

There is no hypothesis.

3.3.5.2 Endpoint Definition

- Total procedure time defined as the period from puncture of the skin performed to obtain venous access for catheter placement to final ECG (electrocardiogram) at end of procedure will be analyzed using descriptive statistics.
- Total fluoroscopy time will be analyzed using descriptive statistics.

3.3.5.3 *Analysis Methods*

A. Statistical Methodology

Tables and descriptive statistics will be used to summarize subject data with respect to these variables. The number of non-missing observations, mean, median, minimum, maximum and standard deviation will be calculated. Summaries for index ablation and re-treatment procedures will be reported separately.

B. Determination of Subjects/Data for Analysis

The population used for descriptive statistics will be the mITT set.

3.3.6 Secondary Objective #6 (Adverse Events/Other)

All adverse events will be summarized.

3.3.6.1 *Hypothesis*

There is no hypothesis.

3.3.6.2 *Endpoint Definition*

All adverse everts that occur during the study will be captured on the CRFs.

3.3.6.3 *Analysis Methods*

A. Statistical Methodology

All adverse events will be summarized by presenting the number of events, the number and percentage of subjects having any AE, having an AE in each body system, and having each individual AE. Any other information collected (e.g., seriousness, severity or relatedness to device/procedure) will be presented as appropriate.

B. Determination of Subjects/Data for Analysis

The population used for descriptive statistics will be the enrolled set. Summaries will be presented for both the Intent-To-Treat (ITT) Set and Modified Intent-To-Treat (mITT) Set.

3.4 Additional Analyses

3.4.1 Additional Analysis Objective #1

Though not defined as an objective in the CIP, a post-hoc analysis on SF-12 Health Survey scores collected at baseline, 6 month, 12 month, 2 year, and 3 year visits will be included in the Final Report.

3.4.1.1 Hypothesis

There is no formal statistical hypothesis associated with this objective

3.4.1.2 Endpoint Definition

There are two endpoints associated with this objective: the SF-12 physical health component score and the SF-12 mental health component score.

3.4.1.3 Analysis Methods

A. Statistical Methodology

The Medical Outcome Study Short Form-12 (SF-12) questionnaire will also be utilized for this objective. The SF-12 questionnaire is a health-related quality of life questionnaire to evaluate the subject's mental and physical performance. For each questionnaire, the physical and mental component scores were calculated using standard scoring algorithms that combine the survey item responses. Both the physical and mental component scores range from 0 to 100, where a 0 score indicates the lowest level of health measured by the scale and 100 indicates the highest level of health.

Summary statistics (e.g. mean, SD, 95% confidence intervals) and graphical methods will be used to describe SF-12 scores from baseline through 36 months. For a subject's physical health score to be calculated at either time point, all physical health dimension questions must be answered; likewise, for mental health scores to be calculated, all mental health questions must be answered. Analysis will be performed on all complete questionnaires from subjects in the mITT dataset.

4 APPENDIX

4.1 Overall Sample Size

In order to adequately power for both the primary effectiveness and safety hypotheses, we require a sample size of 270 evaluable subjects to complete 36 months of follow-up. We estimate that the attrition rate will be approximately 10% per year for the duration of the originally intended 5 year follow-up period. Therefore, the final sample size required to achieve 270 subjects followed for 36 months and account for attrition (i.e. 10% per year) is 370 mITT subjects with procedure attempts. It is expected up to 400 subjects will need to be enrolled to ensure 370 mITT subjects with procedure attempts assuming a small number of subjects who are enrolled will not undergo a procedure.

4.2 General Statistical Considerations

All analyses will be performed using SAS statistical software (SAS Institute Inc, Cary, NC). It is planned that the data from all centers that participate in this protocol will be combined for analysis. Descriptive statistics includes but is limited to number of non-missing observations, mean, standard deviation, median, minimum, and maximum for continuous

variables and count and percentage for categorical variables. Unless otherwise specified, the analysis will be performed using descriptive statistics.

4.3 Interim Subject Safety Monitoring

No formal interim analyses are planned. However, accumulating data for the safety endpoints may be analyzed at any time per regulatory agency's request. Hypothesis statistical testing will not be conducted until the final analysis. No alpha adjustment will be applied in terms of the analysis of the final primary endpoint for all subjects.

Note that incidence rate estimates from analyses for the interim reports may have some upward bias since subjects that recently had a 36-month visit that occurred prior to precisely 36 months will not be part of the risk set (denominator) at 36 months due to being censored at their last follow-up.

4.4 Sensitivity Analyses

In the rare instance where a subject who has your Ablation Catheter System treated but does not meet all inclusion and exclusion, the subject will not be included in ITT and mITT set. If deemed necessary, analyses performed on the mITT analysis set may be repeated based on all treated analysis set to assess sensitivity to the inclusion/exclusion criteria.

4.5 Acronyms

AE	adverse event(s)
AEAC	Adverse Event Adjudication Committee
AF	atrial fibrillation
AFD	atrial fibrillation drug(s)
CI	confidence interval
CIP	Clinical Investigation Plan (protocol)
CPE	cryoablation procedure event(s)
CRF	case report form(s)
CT	computed tomography
CTF	chronic treatment failure
ECG	electrocardiogram
EP	electrophysiology
FDA	Food and Drug Administration
ITT	Intent to Treat population
MAFE	major atrial fibrillation event(s)
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	Modified Intent to Treat population
MRI	magnetic resonance imaging
PAF	paroxysmal atrial fibrillation
PV	pulmonary vein(s)
RF	radio frequency
SAE	serious adverse event(s)
SAP	statistical analysis plan
SAS	Statistical Analysis Systems (software)
SSED	Summary of Safety and Effectiveness Data

STOP-AF	Previous pivotal trial
UADE	unanticipated adverse device effect(s)

4.6 References

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5 VERSION HISTORY

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Jian Huang
2.0	• Replaced assessments scheduled to take place at 5 years to reflect new 3 year timeline of the study replaced 5-year outcomes with equivalent 3-year outcomes. • Modified the statistical methods for center pooling to accommodate 20 – 30 sites (replaced chi square test with Cochran's Q). • Specified details about conducting the tipping point analysis • Removed language pertaining to describing subject screening • Removed additional objectives 1 and 2, which centered around comparing results between this study and the STOP AF Pivotal study, and are now considered out of scope. • Specified an additional analysis describing SF-12 scores at baseline, six months, and at year 1, 2, and 3	Christopher Anderson