Prospective Review of the Safety and Effectiveness of the THERMOCOOL SMARTTOUCH® SF Catheter Evaluated for Treating Symptomatic PersistenT AF (PRECEPT)

IDE # **G140102**

Statistical Analysis Plan

Protocol# STSF-159

Version 4.0

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Revision History

SAP version	Revision Date (DD/MM/YYYY)	List of Changes
2.0	Mar 07, 2017	• Added Section 5.4 Health Economic Data • Added Bayesian adaptive design to select the final sample size of the trial in Section 8.2 • Added Appendix A: Simulation results for the operating characteristics of the trial • Added Appendix B: Simulation R Code
3.0	May 01, 2017	Modified Section 3.0 to add an independent statistician from outside of the sponsor's biostatistics group to conduct the interim analysis
4.0	April 30, 2018	1. Removed Bayesian adaptive design from the following section: • Section 3.0 Study design: "The sample size of the trial will be determined by Bayesian adaptive techniques. …The time of this analysis will not be revealed to study investigators, and the predicted probability of study success or summary results which are calculated at the time of the interim analysis will not be disseminated by the independent statistician performing the interim analysis until the time of the final database lock for the CSR." • Section 8.2 Sample Size: revised to remve the Bayesian adaptive design in sample size decision. • Appendix A & B: removed the whole section regarding the simulation results for the operating characteristics o the trial and the simulation R code.
		2. Added the following section per the template of SAP SOP: • Treatment Assignment • Randomization and Blinding Procedures

		• Interval Windows • Level of Significance • Sample Size Justification: combined sections of sample size and performance goal into this section

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1 Introduction

The purpose of this study is to demonstrate the safety and effectiveness of the THERMOCOOL® SMARTTOUCH™ SF catheter in the treatment of drug refractory symptomatic persistent atrial fibrillation (PsAF) following standard electrophysiology mapping and RF ablation procedures.

This statistical analysis plan contains a detailed description of the statistical analyses and data presentations that will be included in the clinical study report. The statistical methods and analyses described here are based on those presented in Section 7.0 of the study protocol (Version 6.0, 10 April 2018).

2 Study Design

The PRECEPT study is a prospective, multicenter, non-randomized clinical evaluation utilizing the THERMOCOOL® SMARTTOUCH™ SF catheters compared to predetermined performance goals for safety and effectiveness. Up to 367 subjects will be enrolled at up to 35 sites (approximately 30 US and up to 5 OUS).

All patients considered for a RF ablation procedure for drug refractory recurrent symptomatic PsAF should be screened. Subjects who sign the informed consent form will be enrolled in the PRECEPT study and complete the screening assessments. Eligible subjects will undergo pre-procedure assessments within 30 days prior to the initial ablation procedure, which include transthoracic echocardiogram (TTE), imaging for detection of LA thrombus, pregnancy test, electrocardiogram (ECG), baseline 24 hour Holter monitor, baseline medical history, NIH Stroke Scale (NIHSS) assessment, arrhythmias history (including findings from TTM, ECG, Holter monitor, etc.), concomitant cardiac medications (including anticoagulation regime and failed AADs), and baseline quality of life assessment (including AFEQT and Symptoms Severity and Frequency Checklist).

After the index ablation procedure, subjects will enter a 3-Month Medication Adjustment Period followed by a 3-Month Therapy Consolidation Period (Day 0-180). Medication adjustment and repeat ablation may be performed during these periods as necessary.

After the 3-Month Therapy Consolidation Period, the subject will enter the Evaluation Period (Day 181-450). During evaluation period, subjects will undergo follow up visits at predefined intervals to receive study assessments. Subjects complete the PRECEPT study after the 15-month follow up visit.

3 Treatment Assignment

This is a single-arm study and all enrolled patients for the study will be assigned to the study treatment.

4 Randomization and Blinding Proceudres

This study is a non-randomized single-arm study. No randomization or blinding procedure will be performed.

5 Interval Windows

Please refer to the table 5-1 in the section 5.12 of protocol v 6.0.

6 Study Endpoints

6.1 Primary Endpoints and Associated Hypotheses

6.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined as achieving effectiveness success after undergoing an RF ablation procedure using the THERMOCOOL® SMARTTOUCH™ SF catheter.

The null and alternative hypotheses are:

Hypothesis: H_0: $P_E \leq 0.40$

H_a: $P_E > 0.40$

where P_E is the proportion of subjects who meet the effectiveness success criteria at 15 months follow-up

A subject has reached the effectiveness success if the subject is free from documented atrial tachyarrhythmia, including atrial fibrillation, atrial flutter and atrial tachycardia (AF/AFL/AT), recurrence (episodes ≥ 30 secs on Holter recordings/TTM or continuously recorded on the standard 12-leads ECG) during the evaluation period (Day 181-450) and free from the following failure modes:

- Acute procedural failure, including
    - Failure to confirm entrance block in all pulmonary veins post-procedure,
    - Use of a non-study catheter to treat the study arrhythmia for initial ablation,

- Non-study catheter failure while treating the study arrhythmia for repeat ablation procedure during the 3-Month Medication Adjustment or 3-Month Therapy Consolidation Period
- Repeat ablation failure, including
    - >2 repeat ablation procedures during the 3-Month Medication Adjustment Period / 3-Month Therapy Consolidation Period (Day 0-180) after the index procedure,
    - Any repeat ablation procedure during the evaluation period.
- AAD failure: Taking a new AAD or a previously failed AAD at a greater than the highest ineffective historical dose for AF during the evaluation period.
- Surgical failure: Undergoing surgical AF ablation or AF surgery any time after the index procedure.

6.1.2 Primary Safety Endpoint

The primary safety endpoint is the incidence of any primary adverse event (PAE) occurring within 7 days of the AF ablation procedure (including the initial and repeat procedures) using the study catheter per protocol.

The null and alternative hypotheses are:

Hypothesis: H_0: $P_S \geq 0.16$

H_a: $P_S < 0.16$

where P_S is the proportion of subjects with the early onset (within seven days of the initial and repeat ablation procedure for AF) primary AE

PAEs include the following conditions:

• Death • Atrio-esophageal fistula* • Cardiac Tamponade**/Perforation[+] • Myocardial infarction (MI) • Stroke / Cerebrovascular accident (CVA)[†, ††] • Thromboembolism • Transient Ischemic Attack	• Diaphragmatic paralysis • Pneumothorax • Heart block • PV stenosis* • Pulmonary edema (Resipiratory Insufficiency) • Pericarditis • Major vascular access complication / bleeding

* Pulmonary vein (PV) stenosis and atrio-esophageal fistula that occurs greater than one week (7 days) post-procedure shall be deemed Primary AEs.

** Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.

\+ Cardiac Tamponade/Perforation occurring within 30 days of the AF ablation process will be considered Primary AEs

† Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.

†† Modified Rankin score assessments should be made by qualified individuals according to a certification process. If there is discordance between the 30 and 90 day Modified Rankin scores, a final determination of major versus minor stroke will be adjudicated by the neurology members of the Global Safety Monitoring Committee (GSMC).

6.2 Secondary Endpoints

6.2.1 Secondary Effectiveness Endpoints

- Acute Procedural Success: Acute procedural success is defined as confirmation of entrance block in all PVs.
- 15-Month Single Procedure Success
  - The 15-month single procedure success is defined as freedom from documented AF/AFL/AT recurrence (episodes $\geq$ 30 secs) during the Evaluation Period after one single ablation procedure. Any repeat ablation procedure after the initial ablation will be deemed effectiveness failures.
  - The 15-month single procedure success is defined as freedom from documented symptomatic AF/AFL/AT recurrence (episodes $\geq$ 30 secs) during the Evaluation Period after one single ablation procedure. Any repeat ablation procedure after the initial ablation will be deemed effectiveness failures.

6.2.2 Secondary Safety Endpoints

- Occurrence of Early Onset (within 7 days of initial ablation) Serious Adverse Event
- Occurrence of Peri-Procedural (>7 to 30 days) Serious Adverse Event
- Occurrence of Late Onset (>30 days) Serious Adverse Event

6.3 Additional Endpoints

- 15-Month Effectiveness Success - Post Medication Adjustment Period (Day 91-450):
  - All AF Success: Clinical success is defined as freedom from documented all-cause (symptomatic and asymptomatic) AF/AFL/AT recurrence (episodes > 30 secs) between the end of the 3-Month Medication Adjustment Period and the 15-month follow-up visit (Day 91-450).

- Symptomatic AF Success: Clinical success is defined as freedom from documented symptomatic AF/AFL/AT recurrence (episodes ≥ 30 secs) between the end of the 3-Month Medication Adjustment Period and the 15-month follow-up visit (Day 91-450).

- 15-Month Effectiveness Success – Post Therapy Consolidation Period (Day 181-450):
  - All AF Success: Clinical success is defined as freedom from documented all-cause (symptomatic and asymptomatic) AF/AFL/AT recurrence (episodes > 30 secs) during the evaluation period (Day 181-450).
  - Symptomatic AF Success: Clinical success is defined as freedom from documented symptomatic AF/AFL/AT recurrence (episodes > 30 secs) during the evaluation period (Day 181-450).

- Procedural Data:
  - % PV isolation with the study device(s) by PV
  - Repeat Ablation Rate
  - Total Fluoroscopy Time
  - Overall Procedure Time
  - Duration of RF application time
  - RF Ablation parameters per application
  - Device(s) utilized (per ablation)
  - Duration of mapping time
  - VISITAG Settings
  - CF range
  - Power range
  - Ablation index Assessment per anatomical region
  - Ablation index data (Force, Power, and Time) will be collected in the CARTO® 3 system during the ablation procedures. The data will be processed to generate the ablation index.

- Quality of Life (QOL):

  QOL status will be evaluated by assessing AFEQT and arrhythmia-specific Symptom Frequency and Severity Checklist outcomes
  - Quality of Life – AFEQT
  - AF Symptom Frequency and Severity Checklist

- Ablation Strategies Post-PVI:

Ablation strategies post PVI will be recorded during the AF ablation procedure. Safety and effectiveness of the ablation strategies employed post PVI will be characterized.

6.4 Health Economic Data

Health economic data in this study includes:

- The cost and frequency of health care utilization during hospitalization for the study index ablation procedure, as well as any additional hospitalizations during the study period.
- The cost and frequencies of follow up care, including any repeat ablation procedure for treating arrhythmia, necessary procedures/surgeries resulting from procedure, ER visits, and outpatient visits to address issues related to arrhythmia or cardiovascular conditions.

7 Level of Significance

Only primary endpoints will be tested in this study. The hypothesis testing of this study will be performed at a significance level of two-sided 5%.

8 Analysis Sets

For the analysis of study endpoints, the analysis populations are defined as the following:

- **Modified Intent-To-Treat (mITT) Population**: the mITT population will consist of all enrolled subjects who meet all eligibility criteria AND in whom

  (1) RF energy was delivered with study catheter OR

  (2) Study catheter was inserted but no RF energy was delivered

- **Safety Population (SP):** The safety population will consist of all enrolled subjects who have undergone insertion of the study catheter. Safety endpoints will be analyzed based on the Safety Population.
- **Per Protocol (PP) Population:** The PP population will include subjects who satisfy the following criteria:
  - are enrolled and meet all eligibility criteria
  - have undergone RF ablation
  - are treated with the study catheters, and have been treated for the study-related arrhythmia

9 Sample Size Justification

9.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is freedom from documented atrial tachyarrhythmia recurrence without failure modes during the evaluation period (Day 181-450). A performance goal of 40% is set for the primary effectiveness endpoint. Please refer to Section 4.1 of the protocol for justifications of performance goals for the primary effectiveness endpoint.

Based on a performance goal of 40% and an anticipated freedom from AF recurrence rate of 50%, 330 subjects will be required to obtain at least 90% power at a two-sided significance level of 0.05 using the exact binomial method.

9.2 Primary Safety Endpoint

The primary safety endpoint is the incidence of any primary adverse event occurring within 7 days of the AF ablation procedure (including the initial and repeat AF ablation procedure) using the study catheter. A performance goal of 16% is set for the primary safety endpoint. Please refer to Section 4.1 of the protocol for justifications of performance goals for the primary safety endpoint.

Based on a performance goal of 16% and an anticipated rate of 8% for the primary safety endpoint, 232 subjects will be required to obtain at least 90% power at a two-sided significance level of 0.05 using the exact binomial method.

9.3 Total Sample Size

It is estimated that the attrition rate is no more than 10%. In order to obtain 330 subjects, Biosense Webster proposes to enroll 367 (=330/0.90) subjects to account for this potential subject attrition.

10 Statistical Analysis Methods

10.1 General Conventions

- Descriptive statistics for categorical variables will include frequency and percentage. If not otherwise specified, the percentages will be calculated as the number of subjects or events divided by the total number of subjects or events with non-missing data in the specified analysis population. In the calculation of the percentage of subjects having a specific adverse event, the subject will only be counted once even if the subject had the same adverse event multiple times.

- The 95% confidence intervals for proportions will be exact if not otherwise specified.
- The distribution of categorical variables will be compared across multiple groups using the Fisher's exact test.
- Descriptive statistics for continuous variables will include at a minimum, number of subjects, mean, standard deviation, median, minimum and maximum.
- The distribution of continuous variables will be compared across multiple subgroups using Analysis of Variance (ANOVA) or Kruskal-Wallis test depending on the distribution of the variables.
- The Study Day (the number of days since the initial ablation) will be calculated as:

  Study Day = date of the occurrence of event – initial ablation date

  Note: The day of initial ablation is considered Study Day 0. The "event" in the above definition includes: recurrence of atrial tachyarrhythmias, onset of AEs, etc.
- The first 3 months post the ablation procedure is defined as the 3-Month Medication Adjustment Period (Day 0-90), while the following 3-month period is defined as the 3-Month Therapy Consolidation Period (Day 91-180).
- Age is the number of years between the year of birth and the date of informed consent form signed and will be calculated as the integer value of (*year of informed consent signed – year of birth*).

10.2 Subject Disposition

- **Enrolled Subjects**: subjects who sign the informed consent.
- **Excluded Subjects:** subjects who are enrolled but never undergo insertion of the study catheter.
- **Discontinued Subjects**: subjects have the investigational catheter inserted but do not undergo ablation (ie, no RF energy is delivered via the study device). These discontinued subjects will be followed up for 30 days.
- **Lost to Follow-up Subjects:** subjects who are enrolled and have study catheter inserted, but contact is lost after most recent follow-up visit (despite 3 documented attempts.
- **Withdrawn / Early Termination Subjects:** subjects who withdraw consent for study participation or are withdrawn by the investigator or are terminated from the study prior to completion of all follow-up visits.

- **Completed Subjects:** enrolled subjects who completed the 15-month follow-up visit.

Subject accountability and disposition will be summarized descriptively in all enrolled subjects.

10.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all enrolled subjects overall and by sex. Demographic and baseline characteristics will also be summarized for subjects in the safety, mITT, and per protocol populations.

10.4 Primary Endpoints Analyses

10.4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined as achieving effectiveness success at 12 months after undergoing an RF ablation procedure using the THERMOCOOL® SMARTTOUCH™ SF catheter. The primary effectiveness rate will be comparedto a pre-determined performance goal of 40%.

The primary effectiveness endpoint will be evaluated by constructing the two-sided 95% exact confidence interval for the effectiveness rate. If the lower bound of the exact confidence interval of the primary effectiveness endpoint rate is greater than the performance goal of 40%, the study will be considered to have demonstrated effectiveness of the device.

The per protocol population (PP) will be used as the primary analysis population for effectiveness. Subjects with missing effectiveness data during the 15-month follow-up period will be excluded from the primary analysis.

Analyses of the primary effectiveness endpoint will be repeated using the mITT population. Subjects with catheter inserted but no RF deliveried due to investigational device deficiency in the mITT population will be categorized as effectiveness failures and included in the analysis. Subjects with no RF delivery due to other reasons (e.g. anatomical difficulty, complications) will be excluded from the mITT analysis and be included in the sensitivity analysis for missing data.

Sensitivity analyses for missing data will be performed using the PP and mITT populations to assess the impact of missingness on the primary effectiveness outcome and are outlined in section 10.4.3.

10.4.2 Primary Safety Endpoint

The primary safety endpoint is the incidence of any primary adverse event (PAE) occurring within 7 days of the AF ablation procedure (including the initial and repeat procedures) using the

study catheter per protocol. The primary safety rate of the investigational device will be compared to a pre-determined performance goal of 16%.

The primary safety endpoint will be evaluated using the two-sided 95% exact confidence interval for the primary safety rate. If the upper bound of the exact confidence interval of the primary safetyrate is less than the performance goal of 16%, the study will be considered to have demonstrated safety.

The safety population (SP) will be used as the primary analysis population. Subjects with missing primary safety data will be excluded in the primary analysis. Sensitivity analyses for missing data will be performed using the SP and are outlined in section 10.4.3.

10.4.3 Handling of Missing Data

10.4.3.1 Primary Effectiveness Endpoint

Several sensitivity analyses will be performed to assess the robustness of results with regard to missing data for the primary effectiveness outcome. All analyses will be performed in the PP and mITT populations, which include but are not limited to the following:

1) Best-Case Scenario

Subjects with missing effectiveness outcome will be treated as effectiveness success. The point estimate for freedom from recurrence of atrial tachyarrhythmias and the exact two-sided 95% confidence interval will be presented.

2) Worst-Case Scenario

Subjects with missing effectiveness outcome will be treated as effectiveness failure. The point estimate for freedom from recurrence of atrial tachyarrhythmias and the exact two-sided 95% confidence interval will be presented.

3) Multiple Imputation

Multiple imputations will be used to impute missing data for the effectiveness outcome. A multivariate logistic regression model incorporating the demographic and baseline characteristics will be used to impute missing values for the primary effectiveness outcome. Five imputed datasets will be generated. The imputed datasets will then be combined to incorporate both within- and between imputation variability.

4) Tipping Point Analysis

In this study, the tipping point is defined as the number of subjects with recurrent atrial tachyarrhythmia at which the study conclusion is changed. The tipping-point analysis will replace the missing values with effectiveness failures one at a time and the corresponding Z test statistic will be produced. If the Z value is equal to or less than $Z_{1-\propto/2}$, the resulting number of imputed failures is the tipping point. The significance level will be set at α=0.05.

The tipping-point analysis for the effectiveness endpoint will analyze all possible cases that may occur in the missing data cohort. The results will be presented in a summary table to illustrate how p-value and conclusion on meeting the performance goal changes. As listed below, additional analyses may also be performed to assist clinical judgment on whether such a tipping point is implausibly unfavorable.

5) Additional analyses:

- The demographic and baseline characteristics will be compared between cohorts with and without missing data for the primary effectiveness endpoint.
- The reasons for missingness, if available, will be listed for missing data by site.

10.4.3.2 Primary Safety Endpoint

The following sensitivity analyses will be performed in the SP.

1) Best-Case Scenario

Subjects with missing safety outcome will be treated as free from primary adverse events. The point estimate for freedom from early onset primary adverse events and the corresponding exact two-sided 95% confidence interval will be presented.

2) Worst-Case Scenario

Subjects with missing safety outcome will be treated as having experienced a primary adverse event. The point estimate for freedom from early onset primary adverse events and the corresponding exact two-sided 95% confidence interval will be presented.

3) *Tipping Point Analysis*

In this study, the tipping point is defined as the number of subjects with primary AEs for the binary safety endpoint in the study population at which the study conclusion is changed. The tipping-point analysis will replace the missing values with primary AE occurrence one at a time and the corresponding Z test statistic will be produced. If the Z value is equal to or greater than $Z_{\propto/2}$, the resulting imputed number of primary AE is the tipping point. The significance level will be set at 0.05.

The tipping-point analysis for binary safety endpoints will analyze all possible cases that may occur in the missing data cohort. The results will be presented in a summary table to illustrate how Z statistic and conclusion on meeting performance goal changes. As listed below, additional analyses may also be performed to assist clinical judgment on whether such a tipping point is implausibly unfavorable.

4) Additional analyses:

- The demographic and baseline characteristics will be compared between the observed data cohort and missing data cohort. Fisher' exact test will be used for binary variables and Krustal-Wallis test will be used for continuous outcomes as appropriate.

- The reasons for missingness, if available, will be listed for missing data by site.

10.4.4 Subgroup Analysis

10.4.4.1 Site Heterogeneity

Each site should enroll no more than 15% of the total enrollment to minimize the possibility that the study results could be highly influenced by a few sites. Sites with less than five subjects will be combined according to geographic regions. Using this pre-determined criterion, sites with less than five subjects within the same geographic region will be combined such that the combined center(s) would have five or more subjects and no more than 5 sites combined.

A Chi-squre test will be used to examine the homogeneity across sites for the primary effectiveness and safety endpoints. A p-value less than 0.15 will be considered statistically significant for an assessment of heterogeneity across sites. A non-significant result will support pooling of sites for the primary analyses.

If the sites are not poolable, logistic regression models treating site as a random effect will be fit to examine the impact of site heterogeneity on the primary endpoints. This logistic regression will be used as sensitivity analyses.

10.4.4.2 Region Heterogeneity

Approximately 30 US sites and 5 OUS (outside of US) sites will be involved in this study. Up to 30% of subjects may be enrolled at OUS sites and approximately 70% of subjects enrolled at US sites.

A Chi-square test will be used to examine the heterogeneity between regions (US vs OUS) for the primary effectiveness and safety endpoints. A p-value less than 0.15 will be considered

statistically significant for an assessment of heterogeneity between regions. A non-significant result will support pooling of regions for the primary analyses.

If the regions are not poolable, logistic regression models treating region as a random effect will be fit to examine the impact of region heterogeneity on the primary endpoints. This logistic regression will be used as sensitivity analyses.

10.4.4.3 Subgroup Analysis by Sex

In order to reflect the sex ratio of the intended population, Biosense Webster plans to enroll approximately 70% male subjects and 30% female subjects in the study.

Fisher's exact test will be conducted to examine differences in primary safety and effectiveness rates by sex. A p-value less than 0.15 will be considered statistically significant for an assessment of the rate differences by sex. If the test results demonstrate differences by sex, the effectiveness success rate and/or primary AE event rate overall and the 95% confidence intervals will be summarized for each sex group. A logistic regression model treating sex as a fixed effect will be fit to ezamine the impact of sex on the primary endpoint controlling for covariates.

These analyses will be performed in the PP population for the primary effectiveness endpoint and in the SP for the primary safety endpoin

10.4.4.4 Additional Subgroup Anaylsis

In order to provide additional characterization and interpretation of the primary effectiveness and safety outcomes, subgroup analyses based on various prognostic factors may be performed in the PP population for the primary effectiveness endpoint and in the SP for the primary safety endpoint.

10.4.5 Exploratory Anlayses

10.4.5.1 Logistic Regression Analyses

Univariate and multivariate logistic regression analyses will be performed to examine the impact of demographic and baseline characteristics (e.g., age, gender, ethnicity, LA size, AF duration, medical history, etc.) on the primary outcomes. The outcome variables (i.e., primary effectiveness and safety outcomes) will be the dependent variables and baseline and demographic characteristics will be treated as independent variables. Univariate logistic regression models will be conducted for each of the potential predictors. A p-value <0.20 will be the cut-off point for screening covariates. Model selection methods (e.g., forward selection, etc.) will be applied in the multivariate model to identify the best set of predictors for the outcomes. The identification of relevant predictors provides additional characterization and interpretation of

the primary effectiveness and safety outcomes. These analyses will be performed in the PP population for the primary effectiveness endpoint and in the SP for the primary safety endpoint.

10.4.5.2 Time to Event Analysis

Kaplan-Meier curves and survival estimates will be provided for AF/AT/AFL recurrence. This analysis will include all subjects in the PP and mITT and account for censored observations. The survival probabilities of AF/AT/AFL recurrence at 15 months follow-up along with the corresponding 95% confidence intervals using Greenwood's formula will also be presented.

10.5 Analyses of Secondary Endpoints

Descriptive statistics and two-sided 95% confidence intervals using the exact method will be presented for the secondary effectiveness and safety endpoints. No formal statistical hypothesis and inferential statistics will be formulated and performed for the secondary effectiveness and safety endpoints. Analyses of all secondary endpoints will be performed in the proposed analysis populations excluding the subjects with missing outcomes.

10.5.1 Secondary Effectiveness Endpoints

10.5.1.1 Acute Procedural Success

The number and percentage of subjects with acute procedural success and the corresponding 95% exact binomial confidence interval will be presented. Analysis will be conducted based on PP population.

10.5.1.2 15-Month Single Procedure Success

The following analyses will be performed in the PP population:

- The 15-month single procedure success will be presented treating the endpoint as a binary variable. The point estimate and the corresponding two-sided 95% confidence interval will be presented.
- Kaplan-Meier analysis: this analysis will include all subjects in the PP population. Subjects with less than 15-month follow-up will be censored at their last observations.

10.5.2 Secondary Safety Endpoints

10.5.2.1 Occurrence of Serious Adverse Events (SAEs)

Serious AEs will be reported by three timeframes (ablation to ≤7 days, >7 to 30 days, and >30 days post ablation).

- Occurrence of Early Onset (within 7 days of initial ablation) SAE
- Occurrence of Peri-Procedureal (>7 to 30 days) SAE
- Occurrence of Late Onset (>30 days) SAE

The percentage of subjects experiencing the occurrence of serious AEs within each timeframe after the initial ablation procedure and the corresponding 95% exact binomial confidence interval will be presented. Serious AEs in different timeframes will be further evaluated by causality and severity using descriptive statistics. Analysis will be conducted based on safety population.

10.6 Analyses of Additional Endpoints

10.6.1 15-Month Effectiveness Success – Post Medication Adjustment Period (Day 91-450)

The following analyses will be performed for both documented all-cause AF/AFL/AT recurrence and documented symptomatic AF/AFL/AT recurrence in the PP population:

- The 15-month effectiveness success rate post 3-Month Medication Adjustment Period will be presented for subjects in the PP population treating the endpoint as a binary variable. The point estimate and the two-sided 95% confidence interval will be presented.
- Kaplan-Meier analysis: this analysis will include all subjects in the PP population. Subjects with less than 15-month follow-up will be censored at their last observations.

10.6.2 15-Month Effectiveness Success – Post Therapy Consolidation Period (Day 181-450)

The following analyses will be performed for both for both documented all-cause AF/AFL/AT recurrence and documented symptomatic AF/AFL/AT recurrence in the PP population:

- The 15-month effectiveness success rate post 3-Month Therapy Consolidation Period will be presented for subjects in the PP population treating the endpoint as a binary variable. The point estimate and the two-sided 95% confidence interval will be presented.
- Kaplan-Meier analysis: this analysis will include all subjects in the PP population and subjects with less than 15-month follow-up will be censored at their last observations.

10.6.3 Procedural Data

Procedural data such as procedure duration, fluoroscopy duration, power, fluid delivery, output and balance will be summarized with descriptive statistics. These analyses will be conducted using the PP population.

- % PVI isolation with the study device(s) by PV

- Repeat Ablation Rate
- Total Fluoroscopy Time
- Overall Procedure Time
- Duration of RF application time
- RF Ablation parameters per application
- Device(s) utilized (per ablation)
- Duration of mapping time
- VISITAG Settings
- CF range
- Power range

10.6.4 Ablation Index Assessment per Anatomical Region

Ablation index data (force, power, and time) will be collected in the CARTO® 3 system during the procedures. The data will be processed to generate the ablation index and the ablation index will be characterized in the PP population and safety population. Characterization of ablation index may include:

- Descriptive statistics: average, median, min, max, 1st and 3rd quartiles
- Correlation to acute effectiveness and primary effectiveness and safety outcomes where appropriate

10.6.5 Quality of Life

Quality of Life (QOL) status will be evaluated by assessing AFEQT and arrhythmia-specific Symptom Frequency and Severity Checklist outcomes. Descriptive statistics for QOL measurements will be reported. These analyses will be conducted using the PP population.

10.6.5.1 AF Effect on Quality of Life

The AF Effect on QualiTy of life survey (AFEQT) is a questionnaire used to assess the quality of life, specifically for atrial fibrillation patients. AFEQT assess quality of life from three domains, including symptoms, daily activities, and treatment concerns with 18 questions on a seven-point Likert scale. Two additional questions are designed to assess the treatment satisfaction, which will not be included in the overall AFEQT score calculation [1].

The overall AFEQT score and subscales scores for symptoms, daily activities, and treatment concern will be calculated based on the guideline – "Atrial Fibrillation Effect on QualiTy-of-life

(AFEQT) Questionnaire Instruction and Scoring Manual, version 1.0)". Descriptive statistics for the baseline and changes-from-baseline measurements of overall AFEQT score and subscale scores will be presented by follow-up visits.

10.6.5.2 AF Symptom Frequency and Severity Checklist

The symptom frequency score (SFS) and symptom severity score (SSS) will be calculated based on the guideline provided by Bubien, R.S. & Kay, G.N., and revised by Jenkins, L.S., 1993. Descriptive statistics for the baseline and changes-from-baseline measurements of SFS and SSS will be presented by follow-up visits.

10.6.6 Ablation Strategies Post-PVI

Ablation strategies post PVI will be recorded during the AF ablation procedure. Combinations of ablation strategies post PVI will be characterized in the PP population. Characterization of ablation strategies post PVI may include:

- Descriptive statistics: number and percentage of subjects in different ablation strategy
- Acute effectiveness, primary effectiveness and safety outcomes by ablation strategies

10.7 Health Economic Data

The health economic data collected in this study includes the cost and frequency of health care utilization during hospitalization for the study index ablation procedure, as well as any additional hospitalizations during the study period. Because this data does not support the safety and effectiveness of the study catheters and the EPU, it will not be presented in the final report.

11 References

[1] Atrial Fibrillation Effect on QualiTy-of-life (AFEQT™) Questionnaire Instruction and Scoring Manual (2009), Version 1.0, St Jude Medical Inc.