Statistical Analysis Plan (SAP)

Safety and Effectiveness Evaluation of the THERMOCOOL SMARTTOUCH™ SF Catheter with the TRUPULSE™ Generator for Treatment of Paroxysmal Atrial Fibrillation (PAF)

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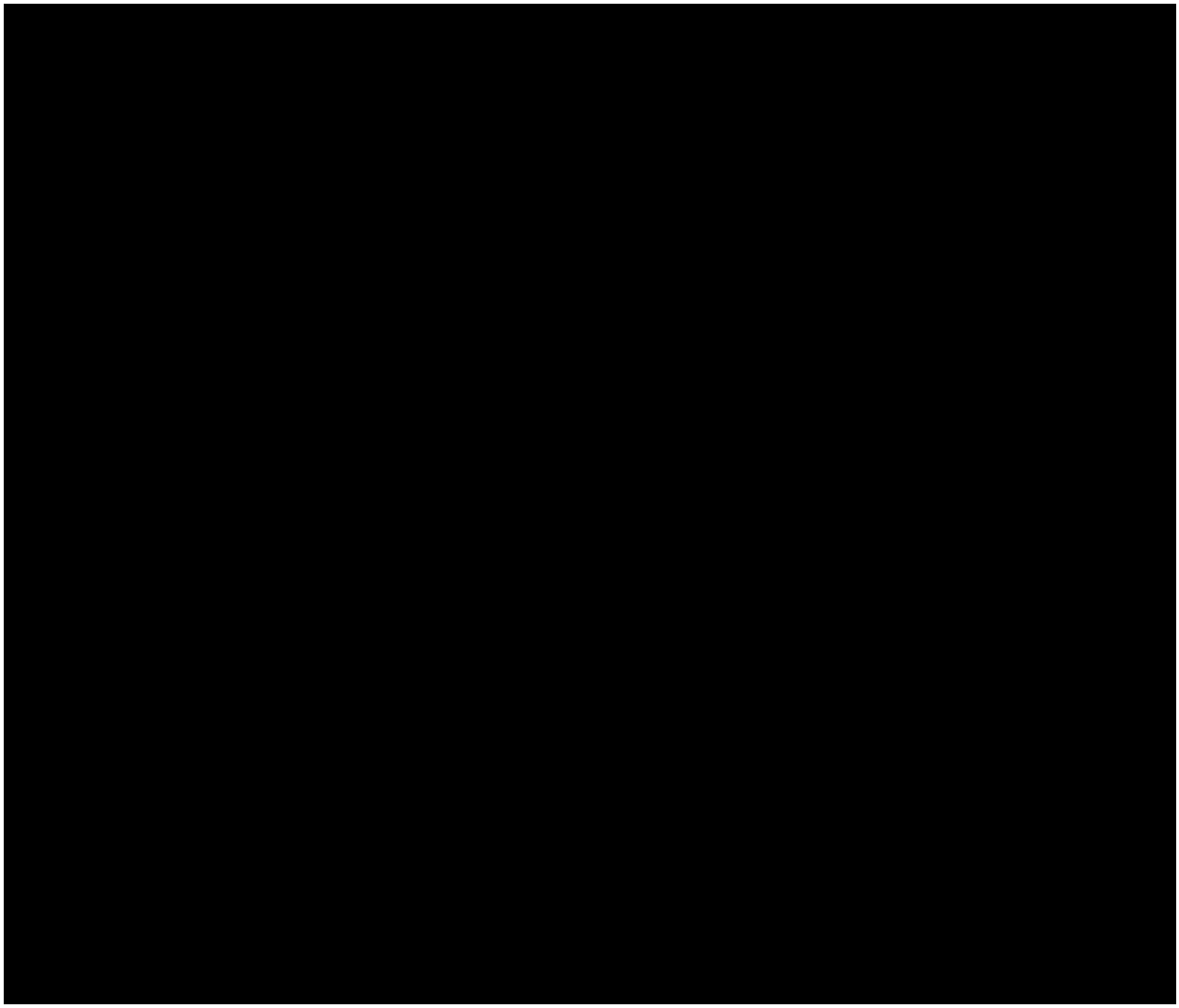
Protocol Version: 3.0

The following individuals have reviewed this version of the Statistical Analysis Plan and are in agreement with the content:

Signature Page



Revision History

Revision Number	Revision Date (DD/MMM/YYYY)	Reasons for Revision
V 1.0	13/JUN/2023	Original document: SAP template version 5.0 implemented.
V 2.0	07/NOV/2023	1. Clarification was added on the definition of Esophageal Endoscopy (EE) analysis set in Section 5.0 2. Clarification was provided for different PVI Durability assessment scenarios in Section 7.1.4. 3. The analysis sets were modified to match what is specified in the CIP in Section 7.7.1 4. The site homogeneity analysis was removed due to not being proposed in CIP. 5. The details of operation definition of AAD failure (Day 105-Day 365) was provided. So AAD failure could be systematically evaluated in Section 7.3.4.3. 6. Acute procedural success was determined based on the targeted veins in which the entrance block could be determined, not on the clinical relevant PV anatomy in Section 7.3.2.

List of Acronyms and Abbreviations

Acronym/ Abbreviation	Expanded Term
AAD	Antiarrhythmic Drug
AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on Quality of Life
AFL	Atrial Flutter
AT	Atrial Tachycardia
CE	Conformite Europeenne
CEC	Clinical Events Committee
CRF	Case Report Form
CT	Cardiac Computed Tomography
CI	Confidence Interval
CIP	Clinical Investigation Plan
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EE	Esophageal Endoscopy
FU	Follow-Up
HM	Holter Monitoring
HRQoL	Health Related Quality of Life
LA	Left Atrial
LTE	Long-Term Effectiveness
mITT	Modified Intent to Treat
MMSE	Mini Mental State Examination
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NA	Neurological Assessment
NIHSS	National Institute of Health Stroke Scale
NSC	Non-Study Catheter
PAE	Primary Adverse Event
PAF	Paroxysmal Atrial Fibrillation
PEE	Primary Effectiveness Endpoint

Acronym/ Abbreviation	Expanded Term
PF energy	Pulsed Field Energy
PG	Performance Goal
PP	Per Protocol
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QoL	Quality of Life
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SP	Safety Population
STSF	Thermocool Smarttouch Surroundflow
USADE	Unanticipated Serious Adverse Device Effect

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1. Study Design

This clinical investigation is a prospective, single arm, multi-center and pre-market clinical evaluation of the Pulsed Field (PF)/Radiofrequency (RF) ablation system (THERMOCOOL SMARTTOUCH™ SF (STSF) Catheter and TRUPULSE™ Generator). The primary objective of this trial is to evaluate the safety and effectiveness of the system for the treatment of Paroxysmal Atrial Fibrillation (PAF).

The study will enroll 135 subjects who have drug refractory symptomatic PAF and are candidates for atrial fibrillation ablation. The study will be conducted at approximately 10 sites in Europe and potentially other regions. The primary safety endpoint is the occurrence of primary adverse events (PAEs) within 7 days of the index procedures, while the primary effectiveness endpoint is the electrical isolation of targeted PVs which will be evidenced by confirmation of entrance block. Both primary endpoints will be evaluated by using the 3-month follow-up data. The hypothesis testing of the primary endpoints will be performed when all subjects completed their 3-month follow-up. A clinical study report (hereinafter, 3-Month CSR) will be submitted as a part of the CE mark application dossier.

All subjects will be followed up for 12 months after their index ablation procedures and be assessed at 7 days, 1-, 3-, 6-, and 12-month scheduled follow-up visits. All study endpoints will be evaluated using the full 12-month follow-up data, except the hypothesis testing of primary endpoints. A clinical study report (hereinafter, Final CSR) will be compiled to present analysis results of all endpoints.

In addition to the main study, there will be four (4) subsets of subjects that will be embedded within the study. The first subset is the Neurological Assessment (NA) subset, which will assess the safety of the procedure in terms of neurological events or complications. The second subset is the Cardiac Computed Tomography (CT) or Magnetic Resonance Angiogram (MRA) image subset, which will assess the occurrence of PV stenosis. The third subset is the Esophageal Endoscopy (EE) subset, which will assess the presence of endoscopically detected thermal esophageal lesions (EDEL) in the region of the contact area between esophagus and LA . The fourth subset is the PVI durability subset, which will assess the durability of the lesion at 2-3 months after the index procedure. The same subjects are selected for all four (4) subsets.

2. Treatment Assignment

All subjects will be treated with the Biosense Webster PF/RF Ablation System, which includes the TRUPULSE™ Generator (D-1417-01-IC), the THERMOCOOL SMARTTOUCH™ SF (STSF) Catheter (D-1348-05-SI-10), and related components and accessories needed for the ablation procedure.

3. Randomization and Blinding Procedures

This is a non-randomized trial with all subjects receiving treatment with the PF/RF ablation system. Therefore, randomization and blinding of treatment assignments for operators and subjects will not be performed. To minimize operational bias, the study will maintain screening logs at each site to ensure that eligible subjects are considered for participation in the study.

4. Levels of Significance

The type-I error for testing each of the primary hypothesis tests is controlled at one-sided 2.5% level. The hypotheses of the primary endpoints will be tested at the full alpha level of 0.025, and only if it is success, the hypothesis testing of the secondary endpoint will be performed at the same alpha level. This gate-keeping approach will control the overall Type I error rate at one-sided 2.5%.

5. Analysis Sets

Analysis sets in this study are defined as the following:

- **Safety Population Analysis Set (SP):** The SP analysis set will include all enrolled subjects who have had the study catheter inserted, regardless of whether energy is delivered or not.

- **Modified Intention-To-Treat (mITT) Analysis Set:** The mITT analysis set will include enrolled subjects who meet the eligibility criteria and have had the study catheter inserted, regardless of whether energy is delivered or not.

- **Per Protocol (PP) Analysis Set:** the PP analysis set will only include enrolled eligible subjects who have undergone the ablation procedure using PF and/or RF energy via the investigational ablation system for the study-related arrhythmia. Subjects who have major protocol deviations that could affect the scientific integrity of the safety and effectiveness will be excluded from the PP analysis set, which includes (but not limited to):

    - Subjects who are found not to meet the eligibility criteria after undergoing the ablation procedure.
    - Subjects who fail in checking entrance block for each targeted PV after adenosine/isoproterenol challenge.
    - Subjects who undergo ablation using the investigational ablation system outside the PV/CTI region
    - Subjects who miss all CIP specified electrocardiographic effectiveness monitoring records.

- **Neurological Assessment (NA) Analysis Set:** The NA analysis set will include all NA subset subjects who have met the additional eligibility criteria specific for the NA subset and have had pre- and post-index-ablation procedure MRI and neurological assessments completed. Subjects who do not have a pre-index ablation procedure MRI assessment but have no lesions observed on post-procedure MRI assessment will still be included for analysis.

- **Esophageal Endoscopy (EE) Analysis Set:** The EE analysis set will include all EE subset subjects who have met the additional eligibility criteria specific for the EE subset and had a readable result of esophageal endoscopy assessment that is done within 1 to 3 days after the index-ablation procedure. Only subjects who have a readable esophageal endoscopy assessment within the specified time frame will be included in analyses for the EE endpoints.

  Note: Endoscopy preferable between 1 day to 3 days (72hours) post procedure. For procedures on Friday, a window of a maximum of 96 hours is justified.

- **Cardiac CT/MRA Analysis Set:** The CT/MRA analysis set will include all CT/MRA subset subjects who have readable outcomes at both baseline and 3 months visit.

- **PVI Durability Analysis Set:** The PVI durability analysis set will include all durability subset subjects who have readable electro-anatomical mapping at the index ablation procedure and have the mapping 75 days (+/-15 days) post index ablation procedure.

Note that discontinued subjects are not subjected to the additional subset assessments (NA, EE, CT/MRA, and PVI durability).

6. Sample Size Justification

- **Primary Safety Endpoint:**

Based on a performance goal of 12% and assuming an anticipated primary safety event rate of 5% for the primary safety endpoint, a sample size of 135 subjects (with 5% missing data due to attrition) will provide above 80% power to reject the null hypothesis for the primary safety hypothesis test using a one-sided exact binominal test. The target significance level is 0.025.

- **Primary Effectiveness Endpoint:**

Based on a performance goal of 90% and assuming an anticipated failure-free rate of 97% for the primary effectiveness endpoint, a sample size of 100 subjects will provide

more than 80% power to reject the null hypothesis for the primary effectiveness endpoint using a one-sided exact binominal test. The target significance level is 0.025.

- **Secondary Effectiveness Endpoint:**

Based on a performance goal of 50% and assuming an anticipated failure-free rate of 65% for the secondary effectiveness endpoint, a sample size of 100 subjects (with 10% missing data due to attrition) will provide above 80% power to reject the null hypothesis test for the secondary effectiveness hypothesis using a one-sided exact binominal test. The target significance level is 0.025.

- **Total Sample size:**

The sample size of this study is mainly driven by the hypothesis test for the primary safety endpoint. The total sample size for this study will be 135 subjects, based on the 135 subjects needed for the primary safety endpoint evaluation, 100 subjects for the primary acute effectiveness endpoint evaluation, and 100 subjects for the secondary effectiveness endpoint evaluation. The sample size estimation assumes a 5% attrition rate of the subjects for the primary safety endpoint and no and 10% attribution of the subjects for the primary and secondary effectiveness endpoints, respectively.

7. Statistical Analysis Methods

7.1 General Conventions

7.1.1 Desriptive Statistics

Standard descriptive summaries for continuous data include the number of observations (e.g., subjects, veins, applications of ablation, etc.) with available data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum values will be presented. For categorical data, the count and percent will be provided. Percentages will be based on the number of observations without missing data.

7.1.2 Handelling Discontinued Subjects in Effectiveness Endpoint Analysis

For all effectiveness endpoints, subjects who are **discontinued** (no energy delivered with the study catheter/system) due to:

- Study system (SMARTTOUCH™ SF (STSF) and TRUPULSE™ Generator) related reasons will be considered acute effectiveness failures.

- Non-study system related reasons (e.g., pump, other equipment or anatomy that precludes treatment with THERMOCOOL SMARTTOUCH™ SF (STSF) Catheter and TRUPULSE™ Generator or a commercially available device) will be deemed as missing the outcome of the acute effectiveness endpoint and excluded from the long-term effectiveness endpoint analyses, including the secondary endpoint.

7.1.3 Handelling Subjects with Specific Ablation Scenarios in Effectiveness Endpoint Analysis

Subjects who undergo ablation using the investigational ablation system or commercial ablation devices at the **PV/CTI regions or outside the PV/CTI regions** will be included in the analysis of acute and long-term effectiveness endpoints according to the following guidelines:

• Condition 1: Subjects who undergo ablation **using the investigational ablation system for PV isolation** will be included in the analysis of acute effectiveness endpoints.

- If the PV isolation is completed using commercial RF (radiofrequency) devices due to reasons related to the study system (SMARTTOUCH™ SF (STSF) and TRUPULSE™ Generator), the subject will be considered a failure for the acute effectiveness endpoint and be included in acute and long-term effectiveness endpoint analyses..

- If the PV isolation is completed using commercial RF devices due to reasons unrelated to the study system (SMARTTOUCH™ SF (STSF) and TRUPULSE™ Generator), the subject will be considered not evaluable for the effectiveness of the investigational system and will be excluded from the analyses of acute and long-term effectiveness endpoints.

• Condition 2: The use of the **investigational ablation system outside the PV/CTI region is not permitted** according to the protocol. Subjects who undergo ablation outside the intended regions using investigational ablation system will be excluded from the long-term effectiveness endpoint analysis, unless they have already failed the acute effectiveness endpoint. Subjects who failed the acute effectiveness endpoint will also be considered failures for the long-term effectiveness endpoint.

• Condition 3: In cases where **commercial RF devices are used for ablation outside the PV region and/or CTI line** to treat arrhythmia identified during the procedure, it is allowed for the well-being of the patient. However, these subjects will be excluded from the long-term effectiveness analysis, as they received additional ablations beyond the intended treatment using non-investigational devices. This exclusion is necessary to avoid mixed effects from non-study devices that could confound the interpretation of the long-term effectiveness results for the investigational devices.

• Condition 4: The **use of the investigational ablation system or commercial RF devices for the ablation of the CTI line to treat documented typical atrial flutter,** identified prior to or during the procedure, is allowed. As the investigational devices are the primary devices used for PV region ablation, these subjects who undergo CTI line ablation will be included in the analyses for acute and long-term effectiveness endpoints.

• In cases where commercial system other than available commercial BWI RF systems are used for repeat ablation during blanking, these subjects will be excluded from the long-term effectiveness analyses unless already failed long-term effectiveness endpoints prior to the repeat ablation.

7.1.4 Handelling Subjects in PVI Durability Subset with Specific Ablation Scenarios in Effectiveness Endpoints Analysis

Subjects in the PVI durability subset that receive PV ablations during the re-map visit will be included in different analyses according to the following guidelines:

For the analysis of Repeat Procedure:

- When an ablation takes place according to the remap results at the PVI durability visit and in the absence of atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL, of unknown origin*), the subjects will not be reported as having a repeat procedure for the repeat ablation procedures related analysis.

For the long-term effectiveness endpoint including Repeat Procedure Failure:

- In cases where a PVI durability visit occurs after 90 days with an ablation for atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL, of unknown origin*) takes place, the subjects will be considered a repeat failure.
- In cases where a PVI durability visit occurs during blanking with an ablation for atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL, of unknown origin*) takes place, the subject will not be considered a repeat

failure. The subject will require >1 repeat ablations at blanking to be considered a repeat failure.

Note: Subjects in the PVI durability subset will be considered LTE failures ONLY IF with a proof of AF,AT or AFL confirmed by electrographic documentation or entrainment maneuvers during the durability assessment. If the ablations are performed due to non-isolated regions in the PV without proof of AF/AT/AFL it will not be considered a repeat procedure.

7.2 Disposition of Study Subjects

Subject disposition and accountability of the study subjects will be summarized descriptively for all enrolled subjects. The definitions of subject disposition categories mentioned in section 19.4.2 of the study protocol will be used to categorize subjects.

7.3 Demographic and Baseline Characteristics

Subject demographics, medical history, previously failed and actively taking AADs utilization and other baseline data will be summarized descriptively for all enrolled subjects. "Previously failed and actively taking AADs utilization" refers to the utilization of anti-arrhythmic drugs by the subjects prior to or at the time of enrollment, including any anti-arrhythmic drugs that the subjects may have taken in the past but did not work to control their arrhythmia and any anti-arrhythmic drugs that the participants are currently taking at baseline.

7.4 Endpoints and Associated Hypotheses

7.4.1 Primary Safety Endpoint

The primary safety endpoint is the occurrence of Primary Adverse Events (PAEs) within seven (7) days of the index ablation procedure where the investigational STSF catheter and TRUPULSE™ generator are used per the clinical investigation plan. The definition of PAEs can be found in section 7.3.1 of the study protocol.

To evaluate the primary safety objective of the study, the PAE rate will be compared against a performance goal (PG) of 12%. The formal hypotheses to test the primary safety endpoint is given as follows:

$$H_0: P_S \geq 0.12 \qquad \text{and} \qquad H_A: P_S < 0.12$$

where P_S denotes the proportion of subjects with primary adverse events.

7.4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint (PEE) is the acute procedural success, which is the achievement of the electrical isolation of targeted PVs at the end of the index procedure. The endpoint is confirmed by the confirmation of entrance block after adenosine/isoproterenol challenge, indicating that there is no electrical conduction from the left atrium into the targeted PVs.

To evaluate the primary effectiveness objective of the study, the acute effectiveness success rate will be compared against a PG of 90%. The formal hypotheses to test the primary effectiveness endpoint is given as follows:

$$H_0: P_E \leq 0.90 \quad \text{and} \quad H_A: P_E > 0.90$$

where P_E denotes the proportion of subjects with acute effectiveness success.

7.4.3 Secondary Effectiveness Endpoint

The secondary effectiveness endpoint is freedom from documented (symptomatic and asymptomatic) atrial arrhythmia episodes including atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL) of unknown origin* during the effectiveness evaluation period (Day 91-365). The AF/AT/AFL episodes will be identified based on electrocardiographic data.

Subjects with an AF/AT/AFL episode that is ≥30 seconds on arrhythmia monitoring device during the evaluation period device are considered failures of this long-term effectiveness endpoint. Acute procedural failure (i.e., failure to achieve entrance block with the study device in any of the targeted PVs) will also be deemed a failure of this endpoint.

To evaluate the secondary objective of the study, the 12-month effectiveness success rate will be compared against a PG of 50%. The formal hypotheses to test the secondary effectiveness endpoint is given as follows:

$$H_0: P_1 \leq 0.50 \quad \text{vs} \quad H_A: P_1 > 0.50$$

where P1 denotes the the proportion of subjects who are failure-free at 12-month follow-up.

**AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-lead electrocardiogram (ECG) or entrainment maneuvers in an EP study.*

7.4.4 Additional Endpoints

No formal statistical hypothesis will be formulated and performed for the additional endpoints. Additional details are described in section 7.11 in the SAP.

7.4.4.1 Additional Procedural Endpoints

- Total procedure time, PVI time, PF/RF application time and mapping time
- Number of PF/RF applications
- Total fluoroscopy time
- Total study catheter left atrial dwell time
- Ablation settings used
- Use of paralytics and type of anesthesia

7.4.4.2 Additional Safety Endpoints

Additional safety endpoints, including SADEs, UADEs and USADEs, SAEs, and non-SAEs:

- Incidence of Serious Adverse Device Effects (SADEs)
- Incidence of Unanticipated (Serious) Adverse Device Effects (UADEs and USADEs)
- Incidence of Serious Adverse Events (SAEs) within 7 days (early-onset), 8-30 days (peri-procedural), and >30 days (late onset) of initial ablation procedure, separately for each timeframe
- Incidence of non-serious adverse events (non-SAEs)

7.4.4.3 Additional Effectiveness Endpoints

- **Single Procedural Success:** defined as freedom from documented symptomatic atrial arrhythmia (AF, AT or AFL of unknown origin*) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365) following a single index ablation procedure. Subjects who had repeat procedure(s) for the study arrhythmia post the index procedure will be deemed failures of this endpoint.

- **Freedom from documented symptomatic atrial arrhythmia (AF, AT or AFL of unknown origin*):** defined as freedom from the documented symptomatic atrial arrhythmia (AF, AT or AFL of unknown origin*) recurrence

based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365).

Acute procedural failure (i.e., failure to confirm entrance block in all PVs except those that are silent and/or cannot be cannulated post-procedure, use of non-study catheter for PV isolation, and failure to have energy delivery with the study device due to ablation system malfunctions) will also be considered a failure.

- **Freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (AF, AT or AFL of unknown origin*) with additional failure modes:** defined as freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (AF, AT or AFL of unknown origin*) based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365). The following criteria will also be deemed failures:

- Failure to achieve acute procedural success.
- Taking a new Antiarrhythmic Drug (AAD) (Class I / Class III) for atrial tachyarrhythmia (AF, AT or AFL of unknown origin*) or taking a previously failed Class I/III AAD at a greater than the highest ineffective historical dose for AF/AFL/AT during the effectiveness evaluation period (Day of 3-month visit* – Day 365).
- Greater than 1 repeat ablation for AF/AT or AFL of unknown origin* in the blanking period or any repeat ablation for AF/AT or AFL of unknown origin* during the effectiveness evaluation period.

**Note: The upper bound of the 3-month visit will be considered as the start point of the evaluation period of AAD failure, which is Day 105. As it is a common practice for medications to be adjusted and/or stopped during an in-clinic visit (i.e., 3-month follow-up visit), subject may have his/her medication adjusted or stopped during the CIP-defined follow-up window, including the Class I/III AADs.*

- **Use of a non-study device** for the purpose of PVI (i.e., touch-up) and/or for the ablation of left atrial non-PV AF targets (i.e., posterior wall) during index ablation procedure or within-lanking repeat procedures.

- **Acute reconnection:** any reconnection in the PVs that are identified after adenosine/isoproterenol challenge among all targeted PVs.

- **Repeat ablation procedures** for left atrial arrhythmia (AF, AT or AFL of unknown origin*) within the 12-month FU period. Procedures for CTI dependent flutter in the follow-up period are not considered repeat procedures per CIP.

- **Quality of Life (QoL):** defined as the change of QoL which is assessed by comparing the Atrial Fibrillation Effect on Quality-of-Life (AFEQT™) scores before and at 3, 6 and 12- months after the ablation procedure.

- **Hospitalization for cardiovascular events** through 12-month follow-up compared to 12 months prior to baseline.

7.5 Analysis of Primary Endpoints

The primary safety and effectiveness endpoints will be evaluated based on 3-month follow-up and procedural data respectively. The hypothesis testing of these primary endpoints will be performed once all subjects treated with the STSF catheter and TRUPULSE™ Generator have completed their 3-month follow-up. The results will be reported and considered as final in the 3-Month CSR. And there will be no updates made to the primary endpoints in the Final CSR. The 3-Month CSR will be submitted as a part of the CE mark application dossier.

7.5.1 Primary Safety Endpoint

The primary safety endpoint will be analyzed using a 3-Month PAE rate. The 3-Month PAE rate is a conservative estimate for the safety rate at the end of the 12-month follow-up. Some PAEs, such as phrenic nerve paralysis, may resolve over time, but for the purpose of the 3-Month CSR, these events will be treated as failures.

The primary safety endpoint will be evaluated using an exact test for a binomial proportion at a one-sided significance level of 2.5%. If the upper bound of the exact two-sided 95% confidence interval of the primary safety endpoint rate is less than the performance goal of 12%, the study will be considered to have demonstrated safety. The study has met its primary safety endpoint.

The hypothesis testing will be performed in the mITT analysis set. Subjects with non-missing PAE outcome data will be included in the primary analysis. The number of events, number of subjects who experience PAEs, and percentage of subjects who experience PAEs will be reported, along with the exact two-sided 95% confidence interval.

To investigate the robustness of the analysis result, sensitivity analyses including estimation of the PAE rate in the SP analysis set, worst-case and best-case scenario analyses, and tipping point analysis will be performed in the SP and mITT analysis sets.

7.5.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint of acute effectiveness success will be evaluated using the exact test for a binomial proportion at a one-sided significance level of 2.5%. If the lower bound of the exact two-sided 95% confidence interval of the acute effectiveness success rate is greater than the performance goal of 90%, the study will be considered to have demonstrated effectiveness. The study has met its primary effectiveness endpoint.

The hypothesis testing will be performed in the PP analysis set. Subjects with non-missing acute effectiveness outcome data will be included in the primary analysis. Subjects who are discontinued (i.e., no energy delivered with the study catheter/system) due to study device related reasons will be considered acute effectiveness failures, regardless of the PV isolation achieved or not. Subjects who are discontinued due to non-study device related reasons will be considered missing outcomes.

To investigate the robustness of the analysis result, sensitivity analyses including estimation of the acute procedural success rate in the mITT analysis set, worst-case and best-case scenario analyses, and tipping point analysis will be performed in the mITT and PP analysis sets. Details are provided in Section 7.6.2.

7.5.3 Criteria for Study Success

Hypothesis testing of the primary safety and primary effectiveness endpoints will be performed when all subjecs have completed at least 3 months of follow-up. The analysis results will be reported in a 3-Month CSR. The study will be considered a success if both primary safety and effectiveness success criteria are met based on the 3-month follow-up data.

Regardless the trail success is achieved ot not based on the 3-month follow-up data, hypothesis testing of both primary endpoints won’t be performed again using the 12-month follow-up data.

7.6 Sensitivity Analyses

The sensitivity analyses will be performed for the primary endpoints based on 3-month follow-up data.

7.6.1 Primary Safety Endpoint

- **Sensitivity to Analysis Set**

The hypothesis testing will be performed in the SP analysis set for the primary safety endpoint.

- **Best-case Scenario**

The PAE rate will be estimated by treating subjects with missing primary safety outcomes as free from primary safety events in the SP and mITT analysis sets.

- **Worst-case Scenario**

The PAE rate will be estimated by treating subjects with missing primary safety outcomes as failures in the SP and mITT analysis sets.

- **Tipping Point Analysis**

Tipping point analysis will be performed for the primary safety endpoint to assess the impact of missing outcomes on the safety conclusion. The PAE rate will be updated one by one by incrementally treating a subject with a missing outcome as failure to evaluate whether a tipping point is identified. If the upper bound of the exact two-sided 95% confidence interval of a PAE rate is greater than the performance goal of 12%, then the tipping point is considered identified. Otherwise, no tipping point is found. The analysis will be performed in the mITT and SP analysis sets.

7.6.2 Primary Effectiveness Endpoint

- **Sensitivity to Analysis Set**

The hypothesis testing will be performed in the mITT analysis set for the acute effectiveness endpoint.

- **Best-case Scenario**

Subjects with missing acute effectiveness outcome data will be treated as a success in this analysis. The proportion of subjects who are acute effectiveness success will be estimated in the PP and mITT analysis sets.

- **Worst-case Scenario**

Subjects with missing acute effectiveness outcome data will be treated as a failure in this analysis. The proportion of subjects who are acute effectiveness success will be estimated in the PP and mITT analysis sets.

- **Tipping Point Analysis**

Tipping point analysis will be performed for the acute effectiveness endpoint to assess the impact of missing outcomes on the effectiveness conclusion. The proportion of subjects with acute effectiveness success will be updated one by one by incrementally treating a subject with a missing outcome as failure to evaluate whether a tipping point is identified. If the lower bound of the exact two-sided 95% confidence interval of an acute effectiveness success rate is less than the performance goal of 90%, then the tipping point is considered identified. Otherwise, no tipping point is found. The analysis will be performed in the PP and mITT analysis sets.

7.7 Subgroup Analyses

In order to provide additional characterization and interpretation of the primary endpoints, the following subgroup analyses will be performed. The mITT will be used for primary safety endpoint and PP analysis set will be used for primary effectiveness endpoint for the subgroup analyses. Descriptive statistics will be presented in each subgroup. No formal statistical hypothesis will be performed to test the differences between subgroups. Descriptive statistics will be presented with the number and proportion of subjects with events by subgroup of the following factors:

- Age group: <65 vs. >=65 years
- Sex: Male vs. Female
- CHA2DS2-VASc Score: ≤2 vs. >2

7.8 Handling of Missing Data

7.8.1 Primary Safety Endpoint

If a subject has had a PAE or is adjudicated by CEC as having a PAE, regardless subject's follow-up duration, the subject will be considered having an event. If a

subject's follow-up time is less than 3 months and the subject has not had a PAE, that subject will be excluded from the primary safety endpoint analysis.

7.8.2 Primary Effectiveness Endpoint

If a subject did not have adenosine/isoproterenol challenge performed or failed in checking entrance block for the targeted vein, the subject will be considered having a missing acute effectiveness endpoint.

7.8.3 Secondary Effectiveness Endpoint

For the secondary effectiveness endpoint analysis, if a subject has an effectiveness failure at any time during the effectiveness evaluation period (Day 91-365), then the subject will be considered to have an event. Subjects who do not experience an effectiveness failure and do not have a full 12-month follow-up and/or sufficient follow-up duration for the secondary effectiveness endpoint (i.e., with at least 335 days of follow-up and arrhythmia monitoring post the index procedure) will be considered missing outcome for the secondary endpoint. These subjects will be censored on the date of their last follow-up for the Kaplan-Meier analysis.

7.9 Adjustments for Multiplicity

The secondary endpoint will only be tested if the primary endpoints are met, using the following hierarchical testing structure:

1. Test the co-primary endpoints, each at α=0.025
2. If fail to reject H_0: $p_s \geq 0.12$ or fail to reject H_0: $p_E \leq 0.50$, then testing is stopped.
3. If reject H_0: $p_s \geq 0.12$ and reject H_0: $p_E \leq 0.50$, then continue to conduct the test of secondary endpoint for H_0: $\mathrm{P12m} \leq 0.50$ at α=0.025.

7.10 Analyses of Secondary Effectiveness Endpoint

If success is achieved in both the primary safety and acute effectiveness endpoints, then the secondary effectiveness endpoint will be evaluated using the exact test for a binomial proportion at a one-sided significance level of 2.5%. If the lower bound of the exact two-sided 95% confidence interval of the 12-Month effectiveness success rate is greater than the performance goal of 50%, the study will be considered to have demonstrated long-term (12-Month) effectiveness. Testing of the hypothesis for the secondary effectiveness endpoint ensures family-wise error rate is controlled at a 2.5% level after the success of the primary endpoints is met.

The secondary effectiveness endpoint will be performed in the PP analysis set when all subjects have completed their 12-month follow-up. The analyses results will be reported in the final CSR

The following additional analysis will be performed for the secondary effectiveness endpoint based on 12-month follow-up data:

- **Sensitivity to Analysis Set**

The secondary effectiveness endpoint will be analyzed in the mITT analysis set as a sensitivity analysis.

- **Kaplan-Meier Analysis**

Kaplan-Meier estimates and plots will be used to characterize the time to first failure event of the secondary effectiveness endpoint, including acute effectiveness failure, recurrence of documented symptomatic/asymptomatic AF/AT/AFL episodes during evaluation period. The probability of freedom from the secondary effectiveness endpoint failure at each follow-up timepoint post blanking will be presented. The KM analysis will be performed in the PP and mITT analysis sets.

- **Best-case Scenario**

The point estimate for freedom from secondary effectiveness failure will be estimated by treating subjects with missing secondary effectiveness outcomes as free from secondary effectiveness events.

- **Worst-case Scenario**

The point estimate for freedom from secondary effectiveness failure will be estimated by treating subjects with missing secondary effectiveness outcomes as failures.

7.11 Additional Endpoint Analyses

No formal statistical hypothesis will be formulated and performed for the additional endpoints. Descriptive statistics will be provided on all additional endpoints in the analysis sets specified below.

7.11.1 Additional Procedural Endpoints

The analyses for the additional procedural data will be summarized descriptively in the mITT and PP analysis sets:

7.11.2 Additional Safety Endpoints

The analyses for the additional safety endpoints, including SADEs, UADEs and USADEs, SAEs, and non-SAEs, will be summarized descriptively in SP and mITT analysis sets as the total number of events, number of subjects with events, and percentage of subjects with events. The SAEs and non-SAEs will be summarized overall and by timepoints of 7 days (early-onset), 8-30 days (peri-procedural), and >30 days (late onset) of initial ablation procedure.

7.11.3 Additional Effectiveness Endpoints

The additional effectiveness endpoints will be summarized descriptively in the PP and mITT analysis sets after all study subjects completed their 12-month follow up.

- **Single Procedural Success:** The number and percentage of subjects with single procedural success will be summarized. Kaplan-Meier estimates and plots will be used to characterize the time to first documented symptomatic atrial arrhythmia (AF, AT or AFL) recurrence following a single index ablation procedure.

- **Freedom from documented symptomatic atrial arrhythmia (AF, AT or AFL of unknown origin*):** Kaplan-Meier estimates and plots will be used to characterize the time to first documented symptomatic atrial arrhythmia (AF, AT or AFL of unknown origin*) recurrence based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365).

- **Freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (AF, AT or AFL of unknown origin*) with additional failure modes:** Kaplan-Meier estimates and plots will be used to characterize the time to first documented (symptomatic and asymptomatic) atrial arrhythmia (AF, AT or AFL of unknown origin*) based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365).

The event-free rate will also be summarized descriptively as the number and percent of subjects free from documented (symptomatic and asymptomatic) atrial arrhythmia (AF, AT or AFL of unknown origin*) during the evaluation period.

- **Use of a non-study device:**
  - The number and percentage of subjects and number and percent of PVs ablated by a non-study catheter (NSC) for PVI will be summarized.
    - Rate of ablation by NSC for PVI among all targeted pulmonary veins during index procedure:

$$= \frac{Number\ of\ PVs\ ablated\ by\ NSC}{Number\ of\ ablated\ PVs}$$

    - Rate of ablation by NSC for PVI among subjects during index procedure:

$$= \frac{Number\ of\ subjects\ with\ at\ lease\ one\ PV\ ablated\ by\ NSC}{Total\ number\ of\ subjects\ ablated\ for\ PVI}$$

  - Ablation of left atrial non-PV AF targets (i.e., posterior wall) during index ablation procedure or for repeat procedures during the blanking period.

$$= \frac{Number\ of\ subjects\ with\ left\ atrial\ non-PV\ AF\ targets\ \ ablated\ by\ NSC}{Total\ number\ of\ subjects\ ablated\ for\ left\ atrial\ non-PV\ AF\ targets}$$

- **Acute reconnection**:
  - Rate of acute PV reconnection among targeted veins:

$$= \frac{Number\ of\ targeted\ veins\ with\ PV\ reconnection\ after\ adenosine/isoproterenol\ challenge}{Total\ number\ of\ targeted\ veins\ with\ adenosine/isoproterenol\ challenge}$$

  - Rate of acute PV reconnection among subjects:

$$= \frac{Number\ of\ subjects\ with\ PV\ reconnection\ in\ at\ least\ one\ PV\ after\ adenosine/isoproterenol\ challenge}{Total\ number\ of\ subjects\ undergone\ PV\ ablation\ procedure\ and\ adenosine/isoproterenol\ challenge}$$

- **Repeat ablation procedures-related endpoints:**
  - Kaplan-Meir estimates and plot will be used characterize the time to the first repeat ablation within the 12-month FU period.
  - Additionally, percentages of subjects with repeat ablation will be summarized by timing of occurrence, including:

1. Percentage of subjects with repeat ablation during blanking period (≤90 days post index ablation procedure)

$$= \frac{Number\ of\ subjects\ undergoing\ repeat\ ablation\ for\ left\ atrial\ arrhythmia\ during\ blanking}{Total\ number\ of\ subjects\ undergone\ index\ ablation\ procedure}$$

2. Percentage of subjects with repeat ablation after blanking period (Day 91 – follow-up 365 post index ablation procedure)

$$= \frac{Number\ of\ subjects\ undergoing\ repeat\ ablation\ for\ left\ atrial\ arrhythmia\ after\ blanking}{Total\ number\ of\ subjects\ undergone\ index\ ablation\ procedure}$$

- PV reconnection identified during the repeat procedure will be summarized:

1. Rate of PV reconnection among previously isolated veins (index):

$$= \frac{Number\ of\ previously\ isolated\ veins\ (index)\ with\ PV\ reconnection\ \ at\ repeat\ procedure}{Total\ number\ of\ previously\ isolated\ veins\ (index)\ in\ subjects\ who\ undergo\ repeat\ ablation\ procedure}$$

2. Rate of PV reconnection among subjects:

$$= \frac{Number\ of\ subjects\ with\ PV\ reconnection\ at\ repeat\ procedure}{Total\ number\ of\ subjects\ undergone\ repeat\ ablation\ procedure\ with\ PVI\ at\ index}$$

- Repeat ablation due to non-PV targets: percentage of subjects with repeat ablations due to non- PV targets

$$= \frac{Number\ of\ subjects\ \ with\ \ non-PV\ reconnection\ at\ repeat\ procedure}{Total\ number\ of\ subjects\ undergone\ repeat\ ablation\ procedure}$$

- **Quality of Life (QoL) :**

Baseline AFEQT scores and changes from baseline at each timepoint the questionnaire is administered will be summarized descriptively for the following five scores. The overall AFEQT score and subscale scores across study visits will also be plotted.

- Overall AFEQT Score (18 questions)
  - Symptom Subscale Score (4 questions)
  - Daily Activities Subscale Score (8 questions)
  - Treatment Concern Subscale Score (6 questions)

- Treatment Satisfaction Score (2 questions)

• **Hospitalization for cardiovascular events**: The number and percentage of subjects and number and percent of hospitalization for cardiovascular event will be summarized.

7.12 Subset Analyses

The same subjects are selected for all four (4) subsets, which include a PVI Durability subset, a Neurological Assessment (NA) subset, a Cardiac Computed Tomography (CT) or Magnetic Resonance Angiogram (MRA) image subset and an Esophageal Endoscopy (EE) subset.

The subset endpoint analysis will be summarized in corresponding subset after all study subjects have completed their 3-month follow up. The analysis results will be presented in the 3-Month CSR. If there are any status change of the endpoint outcome after 3-Month CSR, descriptive summaries will be updated using the 12-month follow-up data and reported in the final CSR.

7.12.1 Analysis of PVI Durability Endpoint

Percentage of targeted PVs in the index ablation procedure being durably isolated as confirmed by the electroanatomical mapping 75 days (+/- 15 days) post index ablation procedure.

Percentage of subjects with durably isolated targeted PVs, as confirmed by the electroanatomical mapping at 75 days (+/- 15 days) post index ablation procedure.

These analyses will be performed in the PVI Durability Analysis Set.

7.12.2 Analysis of NA Endpoint

The following analyses of neurological evaluations will be conducted and summarized descriptively. The analysis will be performed in the Neurological Analysis Set.

In addition to the criteria stated below, subjects will undergo full neurological follow-up only if neurologic symptoms and/or cerebral ischemic lesions are identified in a prior evaluation; results for these additional neurological evaluations will be summarized descriptively.

- **Neurological Exam:** The incidence of new or worsening neurological deficits post-ablation compared to pre-ablation will be summarized descriptively by timepoint.
- **Cerebral Emboli:** The frequency, anatomical location (side and area), and size (diameter and volume) of asymptomatic and symptomatic cerebral emboli observed pre-ablation and new emboli observed post-ablation as determined by MRI evaluations by the core lab will be summarized descriptively by timepoint.

- **Mini Mental State Examination (MMSE):** MMSE scores[2] pre-ablation and change from pre-ablation at the 1-month follow-up will be summarized descriptively and plotted by timepoint.

- **National Institute of Health Stroke Scale (NIHSS):** NIHSS scores[3] pre-ablation and post-ablation prior to discharge will be summarized descriptively and plotted by timepoint.

- **Modified Rankin Scale (mRS):** mRS scores[4] pre-ablation and change from pre-ablation at the 1-month follow-up will be summarized descriptively and plotted by timepoint.

7.12.3 Analysis of CT/MRA Endpoint

Incidence of PV stenosis in the CT/MRA subset up to 3 months post-ablation will be summarized with the number and percentage of subjects and vein level with PV stenosis as defined by the core lab. The analysis will be performed in the Cardiac CT/MRA Analyses Set.

7.12.4 Analysis of EE Endpoint

The number and percentage of subjects experiencing esophageal thermal lesions in the region of the contact area between the esophagus and LA as determined by post-procedure endoscopy and assessed by the core lab will be summarized. The analysis will be performed in the EE Analyses Set.

8. Data Monitoring Committee (DMC)

Data Monitoring Committee (DMC) will assess subjects' data for safety on frequent intervals and make recommendations on study adaptations as described in the DMC Charter.

9. References

1. Spertus, J., et al., Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. Circ Arrhythm Electrophysiol, 2011. 4(1): p. 15-25.

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