Statistical Analysis Plan

A prospective, multicenter, single arm with performance goal study to evaluate safety and effectiveness of Multi-electrode Circular IRE Catheter and Multi-Channel IRE Generator in paroxysmal AF

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V1.0	August 10, 2023	PPD	None
V1.1	April 18, 2024	PPD	1. Two new analysis sets were added for analyzing subjects treated with the investigational device. Analyses related to the effectiveness of the study procedure were required to be based on subjects treated with the investigational device. 2. The analysis of AEs related to the investigational device was removed as analyses were conducted separately for the study catheter and generator.

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Abbreviations

Acronym	Definition
AAD	Antiarrhythmic Drugs
AE	Adverse Event
AF	Atrial Fibrillation
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CEC	Clinical Events Committee
CI	Confidence Interval
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
HRS/EHRA/ECAS	Heart Rhythm Society / European Heart Rhythm Association / European Cardiac Arrhythmia Society
ICF	Informed Consent Form
IRE	Irreversible Electroporation
LA	Left Atrium
LVEF	Left Ventricular Ejection Fraction
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MONOTONE	Monotone Missing
OSA	Obstructive Sleep Apnea
PAE	Primary Adverse Event
PAF	Paroxysmal Atrial Fibrillation
PN	Preferred Name
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Set
WHODRUG	World Health Organization Drug Dictionary

1 Introduction

This document is the Statistical Analysis Plan (SAP) for the statistical analysis of "A prospective, multicenter, single arm with performance goal study to evaluate safety and effectiveness of Multi-electrode Circular IRE Catheter and Multi-Channel IRE Generator in paroxysmal AF". This SAP is based on the AFIRE Study Protocol (Protocol No.: BWI202107, Version No.: 2.2, Version Date: April 20, 2023) and Case Report Form (CRF) (Version No.: 3.0, Version Date: June 2, 2023). It mainly elaborates the specific statistical analysis methods used to analyze and report the baseline characteristics of subjects, the effectiveness evaluation and the safety evaluation.

This document will be updated over time to accommodate Protocol amendments, regulatory and other important changes. This SAP will be finalized and approved prior to database lock. Any deviations from the finalized SAP will be commented in the Clinical Study Report.

1.1 Study objectives

1.1.1 Primary objective

To evaluate the long-term off-AAD effectiveness of BWI IRE system in treatment of patients with symptomatic drug refractory PAF.

1.1.2 Secondary objective

Safety data will be evaluated as a secondary objective.

1.2 Study endpoints

1.2.1 Primary effectiveness endpoint

Long-term effectiveness:

Freedom ≥30 seconds from documented asymptomatic and symptomatic AF, AT, and AFL of unknown origin^{+} based on electrocardiographic data (on ECG or 24h Holter) during the effectiveness evaluation period (91-365 days post index procedure).

If a subject meets any one of the following criteria, then the subject will be considered a long-term effectiveness failure:

a) Failure to achieve acute procedural success. Acute procedural success is defined as confirmation of entrance block in clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) after adenosine and/or isoproterenol challenge.

b) Greater (>) than 1 repeat ablation for AF, AT, and AFL of unknown origin in the blanking period or any repeat ablation or surgical treatment for AF, AT, and AFL of unknown origin during the

effectiveness evaluation period.

c) Non-study catheter failure, including:
    - Use of a non-study catheter (NSC) to treat pulmonary vein targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be canulated) and/or to ablate left atrial non-PV AF targets during the index procedure
    - Use of a NSC to treat pulmonary vein targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be canulated) during repeat procedure in the blanking period

d) Direct current or pharmacological cardioversion for AF, AT, and AFL of unknown origin during the effectiveness evaluation period.

e) Continuous AF, AT, and AFL of unknown origin on a standard 12-lead ECG during the effectiveness evaluation period.

f) A Class I and/or Class III AAD is prescribed for AF, AT, and AFL of unknown origin during effectiveness evaluation period, or end date of Class I and/or Class III AAD past day 90 post procedure.

g) Oral amiodarone is prescribed post index ablation procedure.

[+]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.

1.2.2 Secondary effectiveness endpoints

Secondary effectivenees endpoints include:

- Acute Procedural Success defined as confirmation of entrance block in all clinically relevant targeted PVs after adenosine/isoproterenol challenge. Touching up with focal catheter will be considered as acute procedural failure.
- Acute reconnection identified by adenosine/isoproterenol challenge among all clinically relevant targeted PVs and by subject.
- Rate of PV ablation by a non-study catheter (touch-up) among all clinically relevant targeted PVs and by subject.
- Rate of repeat ablation within the 12M FU period, including timing (blanking period or after blanking) and rate of PV reconnection.

1.2.3 Safety endpoints

Safety endpoints include:

- Procedure and device safety: The incidence of Primary Adverse Events (PAEs) (within seven (7) days of the ablation procedure which uses investigational devices per protocol, including the initial and repeat procedures).
- Occurrence of Serious Adverse Events (SAEs) within 7 days (early-onset), 8-30 days (peri-procedural) and >30 days (late onset) of index ablation procedure.
- AEs and SAEs. AEs will be summarized, including the number of AEs and the number and percentage of subjects experiencing any AEs, the number of all SAEs and all related SAEs and number and percentage of subjects experiencing any SAEs.

1.3 Study summary

1.3.1 Overall study design and plan

This study is a prospective, multicenter, single arm design with a performance goal. All subjects will be evaluated at discharge, 7 days, 1, 3, 6 and 12 months following the index procedure. One early success interim analysis is planned for this study. Study population are patients aged 18-80 with symptomatic drug refractory PAF and indicated for catheter ablation.

A total of 123 non-roll-in subjects will be enrolled. Given at most 2 roll-in cases are planned for each investigator, a maximum of 147 subjects (including 123 non-roll-in and at most 24 roll-in subjects) will be enrolled in this study. All patients will be treated with BWI IRE system and then followed-up for 12 months.

1.3.2 Randomization and blinding

Not applicable.

Prior to locking the database for the planned effectiveness analysis, the study team will not conduct a summative analysis of the primary endpoint of long-term effectiveness. The results of interim analysis will be completed by a third-party independent statistician and reviewed by an independent Data Monitoring Committee (DMC). If the interim analysis does not show early success, the study team will remain blinded to the summary results of the primary endpoint of long-term effectiveness until the study is completed.

1.3.3 Sample size

The sample size of this study is determined by the primary effectiveness endpoint comparing to pre-specified performance goal (PG).

The PG for long-term effectiveness is 50%, based on the minimum acceptable

success rate for PAF at 12-month follow-up as recommended in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of AF.

The hypothesis test for primary effectiveness endpoint is

- H_0: P ≤50% vs.
- H_1: P>50%

Wherein, P is the true long-term effectiveness rate of the investigational device. To test the primary effectiveness rate is greater than the PG value of 50% with at least 80% power, a sample size of 110 evaluable non-roll-in subjects is required assuming the true primary effectiveness rate is 63%, with a one-sided significance level of 0.025, by using Normal Approximation method with Binomial Distribution (using Phat for estimating the variance) (PASS 15.0.5). Given the attrition rate of 10%, 123 non-roll-in subjects will be enrolled. Given at most 2 roll-in cases are planned for each site, a maximum of 147 subjects (including both non-roll-in and roll-in subjects) will be enrolled.

2 Basic considerations for statistical analysis

2.1 General rules

All statistical analyses will be performed based on SAS® 9.4 M6 version.

Statistical analysis will be performed mainly using descriptive statistics. The number of cases, mean, standard deviation (SD), median (first quartile Q1, third quartile Q3), minimum and maximum will be used for continuous variables; and the number of cases and percentage will be calculated for categorical variables. The number of missing will not be included in the denominator for percentage calculation. Table 1 shows the number of decimal places retained for statistical parameters.

Table 1. Number of decimal places retained for statistical parameters

Statistical magnitude	Number of decimal places retained
Mean, Median, Q1, Q3	Retain 1 more decimal place than the original data, up to a maximum of 4 decimal places.
SD, 95% CI	Retain 2 more decimal place than the original data, up to a maximum of 4 decimal places.
Maximum, Minimum	Retain the same number of decimal places as the original data, up to a maximum of 4 decimal places.
Percentage	Retain one decimal place; if the percentage reaches 100%, it is expressed as “100”, if the percentage is 0, it is expressed as “0”.
P value	Retain 4 decimal places; when all 4 decimal places are 0, it is expressed as P<0.0001

2.2 Definition of analysis set

Enrolled subject set: It refers to all patients who have signed ICFs, meet all

eligibility criteria in screening period, and have been successfully enrolled.

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2.3 Rules for data processing

2.3.1 Definition of baseline

Unless otherwise specified, baseline for this study is defined as the result of the last non-missing assessment/examination prior to the start of the index ablation procedure. If a specific time point is not collected, the assessment/examination on the day of procedure is considered to be performed prior to treatment.

2.3.2 Definition of study day

The study day, with the day of index ablation procedure as the reference, is defined as the time interval between the date of event/assessment and the date of index ablation procedure. The day of the index ablation procedure is designated as Day 0 of the study.

Study Day = Date of event/assessment – Date of index ablation procedure

2.3.3 Study periods

The study is divided into a blanking period and an effectiveness evaluation period after the index ablation procedure.

- Blanking period: 1-90 days following the index ablation procedure.
- Effectiveness evaluation period: 91-365 days following the index ablation procedure. Since the visit window for each follow-up is specified in the protocol, i.e., the 12-month visit window is 335-395 days following the index ablation procedure, during the analysis, if a subject's 12-month visit

occurs after 365 days following the index ablation procedure and on or before the end of the protocol-defined 12-month visit window (i.e., ≤ 395 days), all observed failures will be considered as failures in the effectiveness evaluation period.

2.3.4 Definition of analysis window period

Visits during the study will be directly based on the visits recorded in the eCRF. Unless otherwise specified, the observed data will be summarized and analyzed per scheduled visits in the protocol.

All data collected, including data collected at scheduled visits and unscheduled visits, will be presented in the list.

2.3.5 Rules for missing data processing

In the final analysis, a sensitivity analysis for the primary endpoint, missing data will be imputed using multiple imputation.

No imputation will be performed for the missing data on baseline information, procedural information, or secondary effectiveness endpoints.

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2.5 Subgroup analysis

Subgroup analyses will be performed for the primary endpoint in both FAS and SS after the primary endpoint success is achieved. Subgroup analyses will be performed on observed data only. The number of subjects in each subgroup, the number of subjects who achieved primary endpoint success, and the proportion will be presented, and logistic model will be used to calculate odds ratios and

their two-sided 95% CI among subgroups.

- Age (< 65 years, ≥ 65 years)
- Gender (M, F)
- Baseline left atrium diameter (mm) (> median, ≤ median)
- Type of anesthesia during the index ablation procedure
- Activated clotting time (ACT) during index ablation procedure (sec) (<300, [300, 350), ≥350)

2.6 Site merging

Data from all sites in this study will be merged together for analysis and statistical inference.

3 Statistical analysis method

3.1 Basic information of subjects

3.1.1 Disposition of subjects

For all and each site(s), all subjects who signed the Informed Consent Form (ICF) will be summarized for screen success and screen failure, and the reasons for screen failure will also be summarized. The number and percentage of subjects who completed the study and those of subjects who discontinued the study will be summarized based on subjects with screen success. The reasons for study discontinuation will be presented in a table. In addition, the number and percentage of subjects who entered the roll-in analysis set (RI AS), the full analysis set (FAS), the per protocol set (PPS), the safety set (SS), the safety analysis set as treated (SS AT), and the roll-in analysis set as treated (RI AT), as well as the follow-up rate of patients will be summarized.

The information on subject screening and study completion will be tabulated based on all subjects who signed the ICF.

3.1.2 Protocol deviations

Before database lock, protocol deviations will be reviewed and assessed by the investigators and the sponsor and classified as major or minor. Major protocol deviations will be tabulated by type based on the enrolled patient set.

All protocol deviations will be tabulated, and sorted by type of protocol deviation, site, subject ID, and date of deviation.

3.1.3 Demographics and baseline characteristics

Subject demographics and baseline characteristics will be summarized descriptively based on the RI AS, FAS, and SS.

Demographics:

- Age (years)
- Age: < 45 years, [45, 65 years）, ≥ 65 years
- Gender (M, F)

Baseline characteristics:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Pulse (bpm)
- Blood pressure systolic/blood pressure diastolic (mmHg)
- mRS score (0, 1, 2, 3, 4, 5, 6)
- $CHADS_2$ score (points)
- $CHADS_2$ score (points) (0, 1, 2, 3, ≥4)
- CHA_2DS_2-VASc score (points)
- CHA_2DS_2-VASc score (points) (0, 1, 2, 3, ≥4)
- Pre-procedure anticoagulant therapy (Yes, No)
- Pre-procedure left atrial thrombus detection method
- Whether a left atrial thrombus is found (Yes, No)

3.1.4 Cardiovascular medical history

Cardiovascular medical history of subjects will be summarized descriptively based on RI AS, FAS, and SS. Medical history categories not prespecified will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, V25.1 or higher) and summarized by number and percentage according to the System Organ Class (SOC). The denominator is the number of subjects in the analysis set.

The cardiovascular medical history will be summarized by the presence of any known cardiovascular medical history with specific details, the presence of any confirmed embolism and specific type of occurrence, the presence of deep vein thrombosis, and the presence of any cerebrovascular event which is not secondary to embolism.

3.1.5 Other medical history

Other medical history will be summarized descriptively based on RI AS, FAS, and SS. Other medical history includes diabetes mellitus history (type I, type II), obstructive sleep apnea (OSA), abnormal blood routine test results, abnormal

liver function and abnormal renal function. The number and percentage of subjects with other medical history will be summarized according to the specific instructions in eCRF.

3.1.6 Atrial fibrillation history

AF history of subjects will be summarized descriptively based on RI AS, FAS, and SS. The summary will be performed as follows:

- Duration of symptomatic PAF

  Duration of symptomatic PAF (months) = (date of index ablation procedure - date of first symptomatic PAF episode) / 30.4375, wherein 30.4375= (365*3+366)/(4*12).
- In the past 12 months, did the subject experience an episode of PAF
- Methods of identifying AF episodes
- Symptoms related to PAF episodes
- Number of episodes of PAF in the past 12 months
- Average duration of episodes in the past 12 months
- Average frequency of episodes in the past 12 months
- Arrhythmia type other than PAF
- Presence of ablation procedure history
- Number of previous ablation procedures, for subjects with arrhythmias treated by ablation in previous procedures
- Types of arrhythmias treated by ablation in previous procedures
- Time since last ablation (months) = (date of index ablation procedure - date of last ablation procedure) / 30.4375, wherein 30.4375 = (365*3+366)/(4*12).
- Technology used in the last ablation procedure

3.1.7 Assessment of left atrium (LA), left ventricular ejection fraction (LVEF), and pericardial effusion

Findings for baseline LA, LVEF and pericardial effusion will be summarized descriptively based on RI AS, FAS, and SS.

- Method of measurement
- LVEF (%)
- Left atrial diameter (mm)

- Left atrial volume (mL)
- Is any valvular regurgitation observed
  - If yes, valve type
  - Severity of regurgitation
- Pericardial fluid assessment
- Whether there is abnormal heart wall motion

3.1.8 Previous/concomitant therapy

Therapeutic classes will be pre-specified and coded using the World Health Organization Drug Dictionary (WHODRUG, September 1, Version 2022 or higher) and the number and percentage will be calculated by Anatomical Therapeutic Class (ATC) and/or preferred name.

3.1.8.1 AAD medication history

Antiarrhythmic drug (AAD) medication history of subjects will be summarized descriptively based on RI AS, FAS, and SS.

- Previously failed Class I/Class III AADs (Yes, No)
- Reason for failure
- Contraindicated for Class I/Class III AADs (Yes, No)
- Reason for contraindication
- Class I/III AAD treatment failures or contraindications (Yes, No)
- Classes and names of all failed AADs used for atrial fibrillation treatment
- Number of types of failed Class I/III AADs used for atrial fibrillation treatment (continuous variable)
- Number of types of failed Class I/III AADs used for atrial fibrillation treatment (0, 1, 2, 3, 4, ≥5)
- Beta blocker
- Calcium channel blockers

Details of prior Class I/III AAD medication such as the reason for failure, the reason for contraindication, and the historical maximum dose will be tabulated by subject.

3.1.8.2 Other prior/concomitant medications

Other prior/concomitant medications for subjects will be separately summarized descriptively based on RI AS, FAS, and SS. The types of medication and reasons

for medication will be summarized. Meanwhile, medications will be coded using World Health Organization Drug Dictionary (WHODRUG, September 1, Version 2022 or higher), and the number and percentage will be calculated by Anatomic Therapeutic Class (ATC) second level and preferred name (PN).

Other prior medications refer to non-investigational medications that are discontinued before the index ablation procedure.

Concomitant medications refer to non-investigational medications which meet one of the following conditions:

(1) All medications start before index ablation procedure and continue after index ablation procedure.

(2) All medications start on or after index ablation procedure.

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3.1.9 Intra-procedure patient information for index ablation procedure

Index ablation procedure related information will be summarized based on RI AT, FAS, and SS AT.

- Anesthesia type
- Anesthetics
- Using ICE to assess the presence of left atrial thrombus (Yes/No)
  - Presence of left atrial thrombus (Yes/No)

- Is heparin administered (Yes/No)
- Transseptal access
- Which imaging modality is used to guide transseptal puncture
- Sheath type
- Is the Multi-electrode Circular IRE Catheter inserted
- Is a left atrial map acquired prior to PFA
  - If yes, catheter type/imaging method
- PV anatomy
- Is a left atrial voltage map acquired prior to PFA
  - If yes, total mapping duration (min)
- Is PFA applied via the investigational catheter (Yes/No)
- Ablation target
- Total ablation time (min) (defined as the last application time – the first application time)
- Total valid PFA application time (sec)
- Number of valid PFA applications (total, used to ablate PVs, used to ablate non-PVs)
- Study catheter LA dwell time (min) (defined as the time of catheter withdrawal from LA - the time of first catheter insertion in LA)
- Total procedure time (min)
- Total duration of fluoroscopy at end of procedure (min)
- Is a Foley catheter placed
- Fluid delivered via the investigational catheter (ml)
- Fluid delivered intravenously (ml)
- Number of catheter exchange during procedure (in left atrium only)
- Are diuretics given
- What is the subject's heart rhythm at the beginning of procedure
- Is an esophageal monitoring/positioning utilized during the procedure
  - If yes, the monitoring method

- Whether the proximity to the phrenic nerve is evaluated prior to ablation of the right pulmonary vein
- What is the subject's predominant heart rhythm at the end of procedure
- If NOT in sinus rhythm, is cardioversion performed
  - Post-cardioversion rhythm
- Device use
- Number of Multi-electrode Circular IRE Catheters (D-1412-01-SI) used

3.1.10 Pulmonary vein target information during the index ablation procedure

Pulmonary vein target information during the index ablation procedure will be summarized descriptively based on RI AT, FAS, and SS AT, and the summary will be performed as follows:

- Number of valid generator applications
- Valid application locations (ostial, antral)
- Ablation status
- Pulmonary vein isolation
- Observation results
- Is adenosine and/or isoprenaline used to provoke AF prior to verification of entrance block
- Final entrance block
  - If yes, confirmed device

Index ablation procedure targets will be listed by subject. One record is prepared for each patient, including number of applications per PV, PV isolation, and whether conduction block achieved.

3.1.11 Ablation of non-PV triggers and substrate modification

The information on ablation of non-PV AF triggers and substrate modification from the subject's index ablation procedure will be summarized based on RI AT, FAS, and SS AT, including:

- Are any non-PV triggers or substrate modification targets ablated
- Other ablation targets
- Catheter type

- Generator type
- Trigger induced
- Observation results
- Bi-directional block

3.1.12 Compliance with ECG examination and 24-hour Holter monitor

The compliance of subjects with ECG examination and 24-hour Holter monitor at the 3-month, 6-month and 12-month follow-ups after the procedure will be summarized based on RI AT, FAS, and SS AT.

- Number of subjects completing the ECG examination (%)
- Number of subjects completing the 24-hour Holter monitor (%)

3.2 Effectiveness analysis

3.2.1 Effectiveness analysis

The primary effectiveness endpoint is long-term effectiveness. See section "4.1 Interim analysis" for the interim analysis performed for this endpoint. If the interim results meet the early effectiveness success criteria, the interim results will be used for new product registration. The study will continue, and descriptive analyses will be performed at the time of final analysis of the study. If the interim results do not meet the early effectiveness success criteria, the study team will remain blinded to the summary results of primary endpoint of the study, and final analysis, also as the primary analysis, will be performed in the FAS when all non-roll-in subjects undergoing ablation power have completed their 12-month follow-up visit.

3.2.1.1 Primary analysis of final analysis

The effectiveness endpoint is a composite endpoint. All occurrences of the composite events, the earliest occurrence of the composite events will be summarized for each subject. Composite events (refer to the definition of primary endpoint) include:

a) Failure to achieve acute procedural success.

b) Greater (>) than 1 repeat ablation for AF, AT, and AFL of unknown origin in the blanking period or any repeat ablation or surgical treatment for AF, AT, and AFL of unknown origin during the effectiveness evaluation period.

c) Non-study catheter failure, including:

- Use of a non-study catheter (NSC) to treat pulmonary vein targets to achieve isolation of clinically relevant PVs

and/or to ablate left atrial non-PV AF targets during the index procedure

- Use of a NSC to treat pulmonary vein targets to achieve isolation of clinically relevant PVs during repeat procedure in the blanking period

d) Direct current or pharmacological cardioversion for AF, AT, and AFL of unknown origin during the effectiveness evaluation period.

e) Continuous AF, AT, and AFL of unknown origin on a standard 12-lead ECG during the effectiveness evaluation period.

f) A Class I and/or Class III AAD is prescribed for AF, AT, and AFL of unknown origin during effectiveness evaluation period, or end date of Class I and/or Class III AAD past day 90 post procedure.

g) Oral amiodarone is prescribed post index ablation procedure.

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3.2.2 Analysis of secondary effectiveness

All secondary endpoint analyses will be based on RI AT, FAS, and SS AT.

- Acute Procedural Success: the number and percentage of patients with acute procedural success will be calculated, and the two-sided exact 95% confidence interval (CI) will be calculated by the Clopper-Pearson method.
- Acute reconnection: the number and percentage of PVs/subjects with acute reconnection will be calculated, and the two-sided exact 95% confidence interval (CI) will be calculated by the Clopper-Pearson method.
- The number and percentage of PVs/subjects requiring touch-up with a non-study catheter among ablation procedures (including index and repeat ablation procedures); the two-sided exact 95% confidence interval (CI) will be calculated by the Clopper-

Pearson method. Wherein, repeat ablation is defined as any ablation procedure performed after the index procedure, including those recorded during scheduled and unscheduled visits.

- The number and percentage of subjects with repeat ablation procedures during the 12-month follow-up period will be summarized, and the two-sided exact 95% confidence interval will be calculated by the Clopper-Pearson method. The time of repeat ablation (during blanking period, during effectiveness assessment period) and the proportion of PVs/subjects that recovered will be presented. The types of arrhythmias treated with repeated ablation will be presented. Wherein, repeat ablation is defined as any ablation procedure performed after the index procedure, including those recorded during scheduled and unscheduled visits.

3.2.3 Other endpoints

All other endpoint analyses will be based on RI AT, FAS, and SS AT.

- Length of hospital stay for index ablation (days)
- Cardiovascular hospitalization (days)

3.2.4 Exploratory endpoints

- Proportion of patients with long-term effectiveness success with recurrence (AF, AT, AFL) during blanking period.
- Proportion of patients with long-term effectiveness success in single procedure.
- Change in study catheter LA dwell time (min) from the first procedure to the last procedure for surgeons in single-surgeon sites.

3.3 Safety analysis

Unless otherwise specified, all safety analyses will be based on SS.

3.3.1 Adverse Event

Adverse events (AEs) will be coded using MedDRA (V25.1 or higher).

The number of adverse events, the number and percentage of subjects with adverse events will be summarized and analyzed based on the RI AS, FAS and SS:

- Any AE

    - Occurrence of AEs within 7 days (early-onset) of initial ablation procedure
    - Occurrence of AEs within 8-30 days (peri-procedural)
    - Occurrence of AEs >30 days (late onset)
    - Mild
    - Moderate
    - Severe
- PAE
    - Ablation catheter-related
    - Generator-related
    - Ablation procedure-related
- SAE
    - Occurrence of SAEs within 7 days (early-onset) of index ablation procedure
    - Occurrence of SAEs within 8-30 days (peri-procedural)
    - Occurrence of SAEs >30 days (late onset)
    - Mild
    - Moderate
    - Severe
- SAE
    - Leading to death
    - Life-threatening illness or injury
    - Requiring hospitalization or prolongation of existing hospitalization
    - Permanent impairment to the body structure or body function
    - Requiring medical measures to prevent permanent impairment to the body structure or body function
    - Leading to fetal distress, fetal death, congenital abnormality or congenital defect
    - Other
- Serious non-primary AE
    - Occurrence of SNPAEs within 7 days (early-onset) of index

ablation procedure
    - Occurrence of SNPAEs within 8-30 days (peri-procedural)
    - Occurrence of SNPAEs >30 days (late onset)
    - Mild
    - Moderate
    - Severe
- Non-serious AE
    - Occurrence of non-serious AEs within 7 days (early-onset) of index ablation procedure
    - Occurrence of non-serious AEs within 8-30 days (peri-procedural)
    - Occurrence of non-serious AEs >30 days (late onset)
    - Mild
    - Moderate
    - Severe
- Relationship between AE and procedure
    - Definitely unrelated
    - Unlikely related
    - Possibly related
    - Definitely related
- Procedure-related AEs (including: Possibly related and Definitely related)
    - Mild
    - Moderate
    - Severe
- Procedure-related SAEs
- Relationship between AE and ablation catheter
    - Definitely unrelated
    - Unlikely related
    - Possibly related
    - Definitely related

- Ablation catheter-related AEs (including: Possibly related and Definitely related)
  - Mild
  - Moderate
  - Severe
- Ablation catheter-related SAEs
- Relationship between AE and generator
  - Definitely unrelated
  - Unlikely related
  - Possibly related
  - Definitely related
- Generator-related AEs (including: Possibly related and Definitely related)
  - Mild
  - Moderate
  - Severe
- Generator-related SAEs
- AE outcome
  - Symptoms disappeared without sequelae
  - Symptoms disappeared with sequelae
  - Symptoms ongoing
  - Symptoms recovering/resolving
  - Symptoms aggravated
  - Fatal
  - Other
- Intervention or other treatment measures taken for AEs
  - None
  - Medical therapy
  - DC cardioversion
  - Repeat ablation
  - Procedure

- Other
- AEs leading to the study discontinuation for subjects
- Unanticipated AEs
- AEs leading to death
- Death (type of death, cause of death)

A summary of all PAEs and their CEC-adjudicated relationships will be made in the SS.

The number of AEs, the number and percentage of subjects with AEs will be summarized separately by SOC and PT, as well as by severity (mild, moderate, severe) and by onset period (early, peri-procedural, late) in the SS as follows:

- AE
- PAE
- SAE
- Non-Serious AE

In addition, the number of AEs, the number and percentage of subjects with AEs will be summarized by SOC and PT as well as relationship (procedure-related, ablation catheter-related, generator-related) in the SS as follows:

- AE
- SAE
- non-serious AE
- SNPAE
- Unanticipated AE

The relationship includes: Possibly related and Definitely related.

When an AE is described based on the subjects, if the same AE (as distinguished by MedDRA Preferred Term) occurred more than once during the study for the same subject, the subject will be counted only once. Similarly, if an AE occurred more than once in the same System Organ Class for the same subject, the subject will be counted only once in that System Organ Class.

All AEs will be tabulated, recording the name of AE, preferred term (PT), date of index procedure, start date (postoperative days), end date (postoperative days), severity, whether it is a PAE, whether it is an unanticipated AE, whether it is a SAE, classification of SAE, relationship with the procedure (if related to the procedure, whether it is an index or repeat procedure), related to the IRE Catheter, related to the IRE Generator, actions taken for the AE, outcome, date of death,

etc.

Wherein, Postoperative days = AE start/end date – procedure date

3.3.2 Deficiencies of investigational device

Based on RIAS, FAS, and SS, the number and percentage of deficiencies for the investigational device will be summarized by ablation catheter and generator, respectively, including the type of deficiency, time of occurrence of device deficiency, whether the device is returned to the sponsor, whether it leads to an AE.

A list will be presented by subjects and the investigational device.

3.3.3 Other safety analysis

Subjects' mRS scores and changes from baseline at each visit will be summarized descriptively based on RI AT, FAS and SS AT. Shift tables will be used to summarize the change in mRS score (<2, ≥2) from baseline at each visit.

4 Interim analysis and Data Monitoring Committee (DMC)

4.1 CCI

CCI

[redacted]

4.1.1 CCI

CCI

[redacted]

CCI

[redacted]

4.2 Data Monitoring Committee

This study will have a DMC. The established DMC will review the data and put forward recommendations according to the approved study specific charter.

5 Modifications to the original analysis plan

Version 1.1 (Revision date: April 18, 2024)

1. Two new analysis sets were added for analyzing subjects treated with the investigational device. Analyses related to the effectiveness of the study procedure were required to be based on subjects treated with the investigational device.
   - Safety analysis set as treated (SS AT): It includes all the subjects in the SS who have the investigational devices treated.
   - Roll-in analysis set as treated (RI AT): It includes all the subjects in the RI AS who have the investigational devices treated.
2. The analysis of AEs related to the investigational device was removed as analyses were conducted separately for the study catheter and generator.

6 References

Currently none.