Statistical Analysis Plan (SAP)

RAPID-AF: Repetitive Activation Patterns and Focal Impulses Identification and Ablation in Persistent AF using the RHYTHMFINDER-192

Protocol Version: 2.0

SAP Version: 1.0
SAP Date: 09/06/2017

Revision History

Revision Number	Revision Date (DD/MM/YYYY)	Reasons for Revision
N/A		

Table of Contents

1 Study Design

The study is a prospective, single arm, non randomized, open label, multicenter study.

The primary purpose of this trial is to assess safety and effectiveness of using the CARTOFINDER™ (CF) maps created by the RHYTHMFINDER (RF) basket catheter ([redacted]) and the CARTOFINDER™ System using the 4D LAT algorithm in treating persistent atrial fibrillation (PsAF).

Subjects who fulfill the inclusion / exclusion criteria and sign the informed consent form will be enrolled in the RAPID-AF study. Approximately 6-10 centers located worldwide will participate the study. The study will enroll approximately 40 to 70 subjects.

An interim analysis will be performed when 20 evaluable subjects are reached, who have the RHYTHMFINDER™ 192 Catheter inserted and CARTOFINDER guided ablation performed. The interim analysis is not proposed in the protocol. Details of the analysis will be described in the section 10.5.

2 Treatment Assignment

All enrolled patients will undergo the CARTOFINDER™ mapping procedure to identify the ablation targets.

The CARTOFINDER™ 4D LAT Algorithm provides automatic analysis of multiple simultaneous ECG signals recorded by a multi-electrode catheter and leads to the generation of a CARTOFINDER™ Map. The CARTOFINDER™ Map may facilitate the identification of ablation targets including Repetitive Activation Patterns (RAPs) or Focal Impulses (FI) or other ablation targets.

Subjects displaying ablation targets on the CARTOFINDER™ (CF) map will undergo CARTOFINDER™ Guided Ablation (CFGA) and subsequently the PVI (WACA) ablation. Subjects not displaying ablation targets on CARTOFINDER™ will be treated per investigator's standard of care and be followed up 7 days after the ablation procedure.

3 Randomization and Blinding Procedures

Not Applicable.

4 Interval Windows

After the index ablation procedure, subjects will enter a 3-Month Blanking Period (Day 0-90) and then a 9-Month Evaluation Period (Day 91-365). During evaluation period, subjects will undergo follow up visits at predefined intervals (at 7 days, 3, 6, and 12 months post the index procedure) to receive study assessments. Subjects will complete the RAPID-AF study after completing the 12-month follow up visit.

	Screening / Baseline	Ablation Procedure[1]	Discharge	7 Days +/- 2 day	3 Month +/- 1 wks.	6 Month +/- 2 wks.	12 Month +/- 4 wks.
Informed consent[1]	X						
Inclusion & exclusion criteria	X						
Demographics	X						
Medical assessment	X [history]			X	X	X	X
Arrhythmias	X [history]		X	X	X	X	X
ECG (12 lead andCL measurement)	X		X		X	X	X
NYHA/CHADS-VASC2 score	X						
Pregnancy Test[2]	X						
Assessment LA Thrombus[3]		X					
TTE[4]	X						
Ablation assessments		X					
Arrhythmia Monitoring (Holter)[8]					X	X	X
Device Deficiency		X					
Concomitant Medications[5]	X	X	X	X	X	X	X
Adverse events[6]	X	X	X	X	X	X	X

1 Informed Consent to be obtained and collected prior to any study specific assessments
2 Pregnancy test must be done on pre-menopausal women only within 1 week prior to procedure.
3 Imaging method as per standard hospital practice (TEE, ICE,...); within 24 hours prior to procedure
4 Imaging TTE to determine the atrial size (If the subject has undergone an imaging procedure within the last 6-months where the atrial size was assessed, the pre-procedure imaging assessment is not required). If LA diameter is ≥47mm, LA volume to be measured.
5 Concomitant medications: only cardiac related (AAD drugs, anticoegulation regimen, etc.).
6 AEs will be collected once consent has been signed
7 End of study (CRF) page to be completed for ALL enrolled subjects
8 Holter: Dispensation of Holter device at Month 3 visit. 24-hour Holter monitoring at 3 month and ≥72-hour Holter monitoring at 6 and 12 months follow-up.

5 Primary and Secondary Endpoint(s) and Associated Hypotheses

No formal statistical hypothesis was formulated.

5.1 Study Endpoint(s)

Effectiveness

- Acute success defined as: Rate of conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia, after CFGA and PVI (without cardioversion)
- Procedural success defined as: Conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia after overall ablation procedure, with or without the need for cardioversion
- Rate of conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia, after CFGA only (before PVI and without cardioversion)
- Freedom from documented symptomatic AF/AT/AFL recurrence (episodes ≥ 30 seconds on an arrhythmia monitoring device) post the 3-month blanking period through the 12-month follow up.

- Incidence of PVI (confirmed entrance block) after adenosine/isoproterenol challenge
- Change of intra-cycle length from pre-CFGA to post-CFGA and post-PVI

Safety

- Incidence of early-onset Primary Adverse Events
- Incidence of study device and procedural related SAEs during follow-up period (12M)
- Incidence of all SAEs during follow-up period (12M)
- Incidence of study device and procedure related adverse events

5.2 Other Endpoints

- Investigational Device Performance
  - Number of identified CF ablation targets
  - Max number of active RF 192 electrodes during initial mapping procedure
- AAD use post the 3-month blanking period
- Incidence of repeat ablation procedures for AF post the 3-month blanking period
- Procedural data
  - All target sites for RF lesion application
    - Location of ablation targets
    - Number of RF applications per target
    - Total RF duration per application
  - RF ablation parameters (including but not limited to: power, contact force, impedance, flow rate, temperature)
  - Total fluoroscopy time time and dose
  - Total procedure, mapping and ablation time

6 Levels of Significance

No formal statistical hypothesis and inferential statistics will be formulated and performed. Two-sided 95% confidence intervals will be constructed for the effectiveness and safety endpoints.

7 Analysis Sets

The following analyses populations will be used to complete the analyses of the data:

- Safety Subjec t Population (SP): The safety subject population will include all enrolled subjects who have the RHYTHMFINDER™ 192 Catheter inserted, regardless if CARTOFINDER guided ablation was performed.

- Evaluable Subject Population (EP): The evaluable subject population will include all enrolled subjects who have the RHYTHMFINDER™ 192 Catheter inserted and where CARTOFINDER guided ablation was performed.

- Effectiveness Subject Population (EffP): The effectiveness subject population will include all Evaluable Subjects who meet the study eligibility criteria. Effp was not included in the protocol but added in the SAP.

8 Sample Size Justification

This is a feasibility study of safety and effectiveness in which the sample size of the clinical investigation is intended to provide preliminary estimates of these two aspects. Enrollment in the clinical investigation will be approximately 40-70 evaluable subjects.

9 Data Monitoring Committee (DMC)

No Data Monitoring Committee will be constituted for the study.

10 Analyses to be Conducted

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% binomial exact confidence intervals for proportions will be exact if not otherwise specified.

- Descriptive statistics for continuous variables will include at a minimum, number of subjects, mean, standard deviation, median, minimum and maximum.

- The analysis of data will require that the number of days since the initial ablation be calculated. The Study Day will be calculated as: (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.

- Data displays will include three types - summary tables, data listings and figures. Unless stated otherwise, data listings will be produced for all critical data points.

- SAS Studio will be used for the analysis.

10.2 Disposition of Study Subjects

The following subject dispositions are defined:

- Enrolled Subjects: Subjects who have signed and dated the Informed Consent Form.
- Excluded Subjects: Enrolled subjects who have signed an ICF but are found not meeting eligibility criteria prior to insertion of the RHYTHMFINDER™ 192 Catheter.
- Mapping Failure: Enrolled subjects who have the RHYTHMFINDER™ 192 Catheter inserted but inability to record baseline CF mapping signals is observed, will be followed up for 7 days. If an SAE is reported for a mapping failure subject, they will be followed until event resolution or stabilized. The investigator will document mapping failures in the electronic CRF, including reasons for failure.
- Discontinued Subjects: Enrolled subjects who have the RHYTHMFINDER™ 192 Catheter inserted but do not undergo CF guided ablation. If subject's arrhythmia is determined at the time of EP study to be a non-study arrhythmia (required for subject enrollment per study inclusion criteria), the subject will be categorized as discontinued subject. Discontinued subjects will remain in follow-up for 7 days. If an SAE is reported for a discontinued subject, they will be followed until event resolution or stabilized.
- Lost to Follow-up Subjects: Subjects who are enrolled and have the RHYTHMFINDER™ 192 Catheter inserted, but contact is lost after most recent follow-up visit (despite 3 documented attempts to contact the subject).
- Withdrawn / Early Termination Subjects: Subjects who have RHYTHMFINDER™ 192 Catheter inserted but 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 complete the last scheduled follow-up visit per study protocol.

Subject's disposition will be summarized for all enrolled subjects.

10.3 Demographic and Baseline Characteristics

- Demographics

Descriptive statistics for the continuous variable (age) and frequency counts and percentages for the categorical demographics variable (gender) will be summarized for all enrolled subjects.

- Baseline Characteristics

Baseline characteristics, including Medical History Conditions, New York Heart Association (NYHA) Class, $CHADS^2$ score / CHA^2DS^2-VASc score, Persistent AF History, Failed AAD Medicaiton History at screening, Preganancy Test, TTE Exam, Visualization of LA Thrombus assessment, and ECG, will be summarized overall for all enrolled subjects. Descriptive statistics for continuous and categorical variables will be presented.

10.4 Endpoint Analyses

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

- Safety

The incidence of early-onset Primary Adverse Events is the percentage of patients with at least one primary adverse event with onset on Day 0 through Day 7 except for pulmonary vein (PV) stenosis and atrio-esophageal fistula that could occur greater than one week (7 days) post-procedure . The number of primary adverse events and the number of subjects experiencing primary adverse events will be reported.

Incidence of (S)AEs during the 12 month follow-up will be reported as the number of (S)AEs and the number of subjects experiencing (S)AEs. The number and percentage of subjects with (S)AEs will be summarized overall and by AE type, seriousness, severity, relationship to device and procedure, anticipated or not and outcome. Listing of (S)AEs will also be provided.

The SP will be used as the analysis population.

- Effectiveness

Effectiveness outcomes includes

1. Acute Success: Rate of conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia, after CFGA and PVI (without cardioversion)

2. Procedural Success: Conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia after overall ablation procedure, with or without the need for cardioversion

3. Acute Success Post-CFGA: Rate of conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia, after CFGA only (before PVI and without cardioversion)

4. Incidence of confirmed entrance block post-PVI after adenosine/isoproterenol challenge

5. Freedom from documented symptomatic AF/AT/AFL recurrence (episodes ≥ 30 seconds on an arrhythmia monitoring device) post the 3-month blanking period through the 12-month follow up.

6. Change of intra-cycle length from pre-CFGA to post-CFGA and post-PVI

The number and percentages of subjects with effectiveness endpoints (#1- #5) and the corresponding two-sided 95% binomial confidence intervals will be presented.

The descriptive statistics for pre-CFGA, post-CFGA and post-PVI cycle length will be presented. The changes from pre-CFGA cycle length at each ablation procedure steps (post-CFGA and post-PVI) will also be summarized

The EP and EffP will be used as the analysis population for all effectiveness endpoints.

- Other Study Assessments
  - AAD use post the 3-month blanking period
  - Incidence of repeat ablation procedures for AF post the 3-month blanking period

The descriptive statistics for the above endpoints will be summarized in EP.

  - Investigational Device Performance

Investigational device performance will be reported as the number of ablation targets identified and the maximum % of active electrodes. Investigational device performance will also be reported by means of survey questions. Listings of survey answers/scoring will also be provided.

  - Procedural Data

Procedural data including but not limited to procedure duration, mapping duration, fluoroscopy time, RF application time, number of RF application, power, contact force, impedance, temperature, and location of ablation targets will be summarized with descriptive statistics and listed.

These analyses will be conducted in the EP.

10.5 Plans for Interim Analysis

- An interim analysis will be performed when 20 evaluable subjects are reached. Evaluable subjects include those who have the RHYTHMFINDER™ 192 Catheter inserted and CARTOFINDER guided ablation performed. The interim analysis is not proposed in the protocol. The following data will be presented descriptively. Subject enrollment and disposition
- Identified and ablated focal impulse and repetitive activation pattern
- Procedural data
- Adverse event
- Acute procedure success

10.6 Handling of Missing Data

Missing data will be queried for reasons and will not be imputed.

10.7 Sensitivity Analyses

Sensitivity will ber performed for the effectiveness endpoints using the Effectiveness Subject Population.

10.8 Subgroup Analysis

No subgroup analysis will be performed for this study.

10.9 Assessment of Site Homogeneity

Site homogeneity will not be tested in this study.

Appendix: Tables, Listings and Graphs Shells

Please refer to the "RAPID-AF: Repetitive Activation Pattern and Focal Impulses Identification and Ablation in Persistent AF using the RHYTHMFINDER-192. Data Display Table, Figure, and Listing Shells V1.0".

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