Farapulse

FARA-FREE II PMCF Study

Statistical Analysis Plan

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Version History

Version	Version Date	Author/Title	Summary of Key Changes
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1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the FaraPulse FARA-FREE II PMCF study. Study specific details can be found in the Clinical Investigational Plan.

2 Objectives

The purpose of the study is to provide ongoing post-market demonstration of the safety and effectiveness of the FaraPulse system.

2.1 Endpoints

The following primary endpoints for the demonstration of safety and effectiveness are outlined below.

2.1.1 Primary Safety Endpoint

The primary safety endpoint for this study is the Composite Safety Endpoint (CSE) defined as the incidence of the following serious adverse events (SAEs) which are device- or procedure-related, as adjudicated by the CEDMC based on the definitions contained in the Composite Safety Endpoint Definitions as outlined in the CIP.

<u>Early onset (within 7 days of an index or protocol-specified reablation procedure)</u>

- Death
- Myocardial infarction
- Persistent diaphragmatic paralysis
- Stroke
- Transient ischemic attack
- Peripheral or organ thromboembolism
- Pericardial effusion, hemorrhage or tamponade
- Vascular access complications
- Hospitalization
- Heart block

<u>Late onset (any time during follow-up)</u>

- Pulmonary vein stenosis
- Atrio-esophageal fistula

The proportion will be compare to the performance goal (PG) of 17%. The safety hypotheses are as follows:

H_0: $\Pi \geq PG$

H_A: $\Pi < PG$,

where Π is the proportion of subjects with one or more CSE. The null hypothesis will be rejected in favor of the alternative if the upper bound of the 95% binomial exact confidence limit is less than the PG. Sample size is estimated assuming an underlying CSE rate of 9% compared to the PG of 17%. Assuming 80% power and one-sided Type I error of 2.5%, a minimum sample size of 150 is required.

2.1.2 Additional Safety Endpoints

The proportion of subjects:

1. With any adverse event in the Composite Safety Endpoint definitions table, whether or not adjudicated as an SAE
2. With a device- or procedure-related SAE
3. With a device- or procedure-related stroke or TIA
4. With a pre-post cranial MRI change (brain imaging subpopulation)
5. Requiring cardioversion
6. Requiring an arrhythmia-related hospitalization
7. Learning curve analysis.

2.1.3 Primary Effectiveness Endpoint

The proportion of subjects with:

- Acute Procedural Success, AND
- Therapeutic Success, defined as freedom from:
  - Post blanking period through assessment: occurrence of AF, AFL or AT, or ablation for AF/AFL/AT using the study device
  - At any time: ablation for AF/AFL/AT with a nonstudy device

The endpoint will be evaluated using a Kaplan-Meier survival analysis. The freedom from primary effectiveness failure will be estimated at Day 365 and compared to the performance goal (PG) of 50%.

The effectiveness hypotheses are as follows:

H_0: S ≥ PG

H_A: S < PG,

where S is the survival estimate at Day 365. The null hypothesis will be rejected in favor of the alternative if the lower bound of the 95% confidence limit is greater than the PG. Sample size is computed based an expected percent success of 65% vs the PG of 50% using a binomial exact test. Assuming 80% power and one-sided Type I error of 2.5%, a minimum sample size of 85 is required.

2.1.4 Additional Effectiveness Outcomes

1. Acute Procedural Success, defined as the percutaneous endocardial creation of an electrically isolating set of lesions around the ostia of pulmonary veins (PV) during the index procedure, as clinically assessed by entrance and/or exit block performed ≥ 20 minutes after the last PVI lesion is made on a per patient basis.
2. The primary effectiveness endpoint for subjects not on AFDs between Day 105 and the 12 month follow-up visit.
3. First pass isolation (index procedure) consisting of Acute Procedural Success after a single planned set of lesions in each attempted PV
4. The proportion of subjects with early recurrence of atrial fibrillation (ERAF) by 90 days after the initial study ablation
5. The proportion of attempted subjects that achieve Acute CTI Success, defined as the creation of bi-directional electrical block across the cavo-tricuspid isthmus using the investigational devices.
6. Learning curve analysis
7. Rate of any reablation through 12 months of follow-up

3 Statistical Analyses

3.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.3 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required.

3.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and Clopper-Pearson Exact method for categorical variables. Time to event analyses will be reported using Kaplan-Meier graphs.

3.1.2 Study Day

Study Day 0 is the date of the index procedure. Day in study will be calculated relative to the index procedure as follows:

Study Day = Assessment Date – Index Procedure Date

For each subject, duration in study will be based on last study contact date which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit including date of death.

Duration variables will be calculated as follows:

Duration Days = Start Date – End Date

3.1.3 Visit Windows

Unless otherwise specified, visit based assessments will be analyzed for each analysis time point according to the nominal visit entered in the Case Report Form (CRF) regardless of if it is out of window.

3.1.4 Statistical Significance

No formal hypothesis tests will be conducted. Any p-values reported will be descriptive and will be performed at the two-sided 0.05 significance level. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001". If a p-value is greater than 0.999, it will be reported as ">0.999".

3.1.5 Precision

Unless otherwise specified, the following conventions will apply for data display. In general, percentages will be displayed to 1 decimal place. Percentages <0.05% will be reported to 2 decimal places. For continuous parameters, means and medians will be reported to 1 additional decimal place than the measured value while standard deviation will be reported to 2 additional decimal places than the measured value. Minimum and maximum values will be reported to the same precision as the measured value.

3.2 Analysis Populations

The following analysis populations are defined for analysis:

1. **ITT**: The ITT analysis set is defined as all enrolled subjects except those who terminate their participation prior to the beginning of the Index Procedure

The primary safety and effectiveness analyses will be summarized in the ITT analysis set.

3.3 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all clinically-relevant baseline demographic, medical history, and clinical characteristic variables.

3.4 Analysis of Study Endpoints

3.4.1 Primary Safety Endpoint

The primary safety outcome is the Composite Safety Endpoint (CSE) defined as the incidence of the following early-onset and late-onset serious adverse events (SAEs) which are device- or procedure-related, as adjudicated by the CEDMC.

3.4.1.1 Primary Analysis

The endpoint will be evaluated using the ITT analysis set. The endpoint will be presented as the frequency and percent of subjects experiencing one or more CSE as well as the total number of events.

The numerator will include subjects with one or more CSE and the denominator will include all ITT subjects. The individual components of the CSE will also be summarized.

The proportion will be compared against the performance goal (PG) of 17%. The endpoint will be met if the upper bound of the 95% exact binomial CI around the proportion is less than the PG.

3.4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is Acute and Therapeutic Success evaluated with a survival (KM) analysis.

3.4.2.1 Primary Analysis

The endpoint will be evaluated using the ITT analysis set. The endpoint will be presented using Kaplan-Meier survival analysis. The number of subjects at risk and the survival estimate will be presented at 30 day intervals from the index procedure date through Day 365.

For subjects with an event, the date of the first event occurrence will be used as the basis for event time. For subjects without an event, the date of censoring will based on date was last evaluable for the endpoint. If a subject's censoring time without event is at or after the window open date of the month 12 visit window, the censoring time will be set to Day 366.

3.5 Additional Analyses

3.5.1 Procedural Outcomes

The following procedure characteristics will be summarized in the ITT cohort on a per subject basis.

1. Assessments of duration for procedure components
    a. Procedure time (initiation of venous access to venous access closure).
    b. Dwell time (sum of catheter entry-to-exit durations).
    c. Total ablation time (first ablation to last ablation)
    d. Fluoroscopy time (total duration of exposure).
2. Characterization of lesion sets:
    a. PVI ablations
    b. Extra-PV ablations, excluding CTI ablations
    c. CTI ablations
    d. Anomalous PV ablations