ST. JUDE MEDICAL

STATISTICAL ANALYSIS PLAN SIGN OFF FORM

RD + AF Clinical Study
Statistical Analysis Plan Rev A

REVIEWED AND APPROVED

Carlye Kraemer

Carlye Kraemer, Sr. Biostatistician — 05NOV2014 — Date

Andrew Campbell

Andrew Campbell, Clinical Project Manager — 05 Nov 2014 — Date

Angie Roach

Angie Roach, Sr. Director Clinical Research — 05-NOV-2014 — Date

Statistical Analysis Plan

A feasibility study to evaluate the effect of concomitant renal denervation and cardiac ablation on AF recurrence (RD+AF)

SJM-CIP-0009

Table of Contents

1 INTRODUCTION

1.1 Purpose

The purpose of this Statistical Analysis Plan is to provide guidance for analyses associated with the RD+AF Clinical Trial (Agile# SJM-CIP-0009).

1.2 Scope

This plan describes the study specific statistical analyses required for the RD+AF trial.

1.3 Definitions

Role/Term	Definition
SJM Clinical Team (SJMCT)	Those individuals working within the GCAO clinical affairs department at the project manager level or lower (e.g. Clinical Project Manager, CRAs, CRCs, etc.)
Field Clinical Engineers (FCE)	Those individuals providing EnligHTN procedure training, case coverage, and other administrative support. For the purposes of this document, this refers to FCE Directors, FCE Managers, and all other levels of FCEs that have been assigned to work on the RD+AF trial.
Monitor	This is a subset of the SJM personnel or CRO personnel who have received monitoring training outside of this plan. They are responsible for oversight of specific study sites and will be performing on-site monitoring visits. They may or may not be part of the SJMCT.
Site Personnel (Site)	Those individuals working as part of the RD+AF trial as an employee or agent of the study site.
Data Management Personnel (DM)	Those individuals working within the Data Management group at SJM in the GCAO (e.g. database developers and report programmers)
Vendor (V)	Any non-study site entity outside of SJM that has been contracted to perform services or provide equipment for study execution.
Statistics (Stats)	Those individuals within the Biostatistics group at SJM in the GCAO that are involved with the trial.
Safety Personnel (Safety)	Those individuals within the Clinical Safety group of the GCAO at SJM that are involved with analysis and reporting of adverse events.
Regulatory (Reg)	Those individuals within the Regulatory Affairs group at SJM in CATD that are involved with the trial.
Trial Master File (TMF)	Electronic files kept in Windchill

For any other terms, please consult the RD+AF clinical investigation plan (#SJM-CIP-0009).

2 STATISTICAL ANALYSIS

2.1 Study design

This is a post market, prospective, multicenter, 2:1 randomized study of the EnligHTN™ Renal Denervation System in conjunction with atrial fibrillation ablation. Up to one hundred subjects with paroxysmal or persistent atrial fibrillation and uncontrolled hypertension will undergo atrial fibrillation ablation. Per the 2:1 randomization, a minimum of 50 or 2/3 of the total patient cohort will also undergo renal artery ablation. Subjects will be followed up to two (2) years post procedure.

To assess the feasibility of concomitant cardiac ablation for the treatment of atrial fibrillation and renal denervation ablation using the EnligHTN renal denervation system in achieving freedom from atrial fibrillation in patients with hypertension. Freedom from atrial fibrillation

will be assessed based on electrocardiographic data during nine months following the blanking period.

2.2 Sample size estimation

The sample size of 75 patients is used considering the study purpose: to complete a preliminary evaluation on whether or not concomitant renal denervation with the EnligHTN™ Renal Denervation System and cardiac ablation will result in improved outcomes as compared to ablation alone in patients being treated for Atrial Fibrillation. Of these patients, a minimum of 50 patients (or 2/3 of the total patient cohort) will undergo both a cardiac ablation procedure and a concomitant renal denervation procedure.

No formal power analysis or hypothesis test will be performed. However the data collected will be analyzed and presented using the descriptive or appropriate summary statistics.

All patients who have signed a Patient Informed Consent (PIC) will be considered enrolled in the study.

However, the Primary Analysis population will only include those patients that have signed a PIC, have undergone a cardiac ablation procedure for the treatment of atrial fibrillation, and, if in the renal denervation arm of the study, had the EnligHTN™ Renal Denervation System enter his/her body.

It is anticipated that there may be subjects who have been enrolled in the study but are not included in the Primary Analysis population, such as:

- Subjects who are enrolled but do not meet baseline inclusion or exclusion criteria before the procedure; these are considered the screen failure population.
- Procedurally excluded populations will include subjects who have enrolled in the study and start the procedure, but do not undergo a cardiac ablation procedure for the treatment of atrial fibrillation or if in the renal denervation arm of the study and do not have the EnligHTN™ Renal Denervation System enter his/her body, due to their anatomy, circumstances related to the procedure, or physician judgment.

Subjects who withdraw from the investigation will not be replaced in any analysis population. All available data from these subjects will be included in summary statistics and analyses where applicable.

2.3 Data Analysis and Reporting

Data analysis will be performed across all subjects based on Primary Analysis population unless otherwise specified.

The data collected will be presented using the appropriate summary statistics. Continuous data will be summarized using descriptive statistics (mean, number of observations, standard deviation, minimum and/or maximum values) and categorical data will be summarized using frequencies and percentages.

2.4 Primary objective

The primary objective is to assess the feasibility of concomitant cardiac ablation for the treatment of atrial fibrillation and renal denervation ablation using the EnligHTN renal denervation system in achieving freedom from atrial fibrillation in patients with hypertension.

The freedom from atrial fibrillation will be assessed based on electrocardiographic data during nine months following the blanking period including the one week recording coinciding with the 12 month follow-up visit (9 months following the 3 month blanking period). AF recurrence during the blanking period will not qualify as an endpoint event per protocol. Subjects may be re-treated with up to two repeat ablation procedures during the course of the study with a 3 month blanking period following the treatment. Assessment of the AF recurrence will be determined through evaluation of 12 lead ECG recordings, holter monitoring or event recorder results. AF Recurrence is defined as episodes lasting longer than 30 seconds in duration unless detected via 12-lead EKG. To count as a study-related recurrence, the AF episode must be documented on the AF Recurrence Evaluation CRF. For this study, AF also includes (documented >30 seconds) atrial flutter and atrial tachycardia.

No formal hypothesis testing will be performed. An overall percentage of subjects experiencing an event will be summarized for each randomization arm and is defined as:

$$\frac{Number\ of\ subjects\ with\ AF\ recurrence\ within\ 12\ months\ post\ procedure}{Number\ of\ subjects\ with\ at\ least\ 12\ months\ of\ follow-up\ or\ experienced\ AF\ recurrence} * 100$$

Subjects who exit the study prior to 12 month visit without AF recurrence will be excluded from the percentage to prevent under-estimation of the event rate. Kaplan-Meier analysis may be performed to provide freedom from atrial fibrillation rates at one year for each randomization arm using date of ablation procedure to date of first event.

2.5 The Secondary objectives

2.5.1 Safety Acute data

The major adverse cardiac events (MACE) within 7 days post procedure will be summarized as a percentage of patients as defined as:

$$\frac{Number\ of\ subjects\ with\ major\ adverse\ cardiac\ events\ within\ 7\ days\ post\ procedure}{Number\ of\ subjects\ with\ at\ least\ 7\ days\ of\ follow-up\ or\ who\ experienced\ an\ event} * 100$$

The denominator includes subjects who either had an event within 7 days post procedure or were eligible to meet the endpoint, i.e. followed through at least 7 days.

The peri-procedural events will be summarized as a percentage of patients as described below. Rates will be calculated for each randomization arm.

$$\frac{Number\ of\ subjects\ with\ at\ least\ one\ event\ within\ 30\ days\ post\ procedure}{Number\ of\ subjects\ with\ at\ least\ 30\ days\ of\ follow-up\ or\ who\ experienced\ an\ event} * 100$$

All serious and possibly device or procedure related adverse events are reported and adjudicated by an internal medical expert. An event is considered a MACE if it meets the criteria defined in the Adverse Event Adjudication Plan.

2.5.2 Safety Midterm (6 months) and Long term (1-2 years) data

For all patients, the major adverse cardiac events will be recorded and summarized at 6 months, 1 year, and 2 years. Event rates will be calculated for each arm as the number of subjects who experienced a major adverse cardiac event over the number of subjects who experienced an event within or were followed to each time interval. Kaplan-Meier analysis may be performed for time to first major adverse cardiac event.
For patients undergoing the renal denervation procedure:

- The new (or worsened) renal artery stenosis (>50%) and/or aneurysm at the site of ablation per Renal Artery Imaging will be summarized at 6 and 12 months. A percentage of patients who have new stenosis and/or aneurysm compared to baseline will be provided. The denominator includes subjects with a baseline and follow-up assessment at the corresponding interval. Image interpretation will be based on local analysis. Kaplan-Meier analysis may be performed if applicable on the time to the first new renal artery stenosis and/or aneurysm at the site of ablation.
- Renal function change based on eGFR will be summarized by computing the change of the eGFR at 6 months, 12 months and 2 years compared to baseline (follow-up interval – baseline) for each patient with data available in both time points. The mean and standard deviation of the eGFR change at those intervals will be presented.
- Overall renal vascular safety will be summarized as a rate of subjects with a serious, device or procedure related event over total subjects randomized to the renal denervation group at each follow-up time point.

2.5.3 AF Recurrence

The primary endpoint will evaluate recurrence of AF during the 9 months following the blanking period for each group. Secondarily, the recurrence of AF based on electrocardiographic data at 3 months, 6 months and 24 months post procedure will also be reported by group. The rate of AF recurrence will be calculated using the same definition as the primary objective for the specified time points.

- Assessment of the AF recurrence will be determined through evaluation of 12 lead ECG recordings, holter monitoring or event recorder results. AF Recurrence is defined as episodes lasting longer than 30 seconds in duration unless detected via 12 Lead EKG. To count as a study-related recurrence, the AF episode must be documented. For this study, AF recurrence also includes (documented $\geq$30 seconds) atrial flutter and atrial tachycardia.

2.5.4 BP reduction

The mean reduction of office systolic BP, office diastolic BP, and ambulatory BP parameters at six (6) months will be analyzed by computing the reduction of BP measurements compared to baseline (6-month – baseline) for each patient with data available in both time points. The mean and standard deviation of the BP reduction will be summarized for each group.

Blood pressure parameters at 12 and 24 months post procedure will be calculated in the same way as described in the calculation of the reduction at 6 months.

The percentage of subjects achieving office SBP < 140 at 6 months visit will be computed for each group as follows:

$$\frac{Number\ of\ subjects\ achieving\ office\ SBP\ <\ 140\ at\ 6\ months\ visit}{Number\ of\ subjects\ \ with\ \ data\ available\ in\ 6\ months\ visit} * 100$$

2.6 Other Analyses

In addition, subgroup analyses may be performed as needed, e.g.:

- for subjects that have the renal denervation procedure performed on one side but not the other (due to their anatomy, circumstances related to the procedure, or physician judgment)
- based on the number of ablation points performed
- by the subject's primary disease conditions at baseline.

Ad hoc analyses may be performed as needed. Analysis may be performed based on As Treated population as appropriate. In general, data analysis will be performed on a per subject basis, but the data analysis may be presented per kidney, or on renal artery basis, as appropriate.

2.7 Analysis Software

The statistical analyses will be performed using SAS™ software version 9.3, or as specified and appropriate.