ReCor Medical

Pooled Statistical Analysis Plan for Publication

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Version History

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1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to for an individual patient-level meta-analysis of three independently established, international, prospective, randomized, sham-controlled clinical studies of the ReCor Medical Paradise System for renal denervation in subjects with hypertension:

- RADIANCE-HTN
    - SOLO cohort
    - TRIO cohort
- RADIANCE II

These studies were selected due to their adherence to the FDA/ASH consensus on trial designs for renal denervation trials of hypertension which included: standardized design (prospective, randomized, sham controlled with the same primary endpoint at 2 months), use of the same renal denervation technology and technique, consistent study monitoring and data collection (i.e. standard instruction and data collection regarding medications, blinded clinician follow-up, blinded core lab for Ambulatory Blood Pressure Monitoring (ABPM)).

For the purposes of this analysis plan, each of the three studies above (SOLO, TRIO, and RADIANCE II) will be referred to as “studies” in this SAP since each had its own inclusion/exclusion criteria and randomization schema.

2 Study Objectives

The purpose of this analysis is to provide summary effectiveness and safety estimates from pooled data of independently established, international, prospective, randomized, sham-controlled clinical studies of the ReCor Medical Paradise System for renal denervation in subjects with hypertension across trials with similar designs, operational implementation, and follow-up.

3 Study Design

This is a pooled analysis of individual patient data from independently established prospective randomized controlled trials. For the RADIANCE-HTN study, the two cohorts (SOLO and TRIO) are treated as separate cohorts (equivalent to treating them as separate studies) given the specific inclusion/exclusion criteria for each cohort, the fact that each cohort was independently powered and enrolled, and had separate randomization schemes.

Selection of included studies was based on prospective, randomized, sham-controlled, international studies of renal denervation in subjects with hypertension. Studies of different denervation

technologies, studies without a sham control, or studies specific to one country are excluded. Studies were selected due to their adherence to the FDA/ASH consensus on trial designs for renal denervation trials of hypertension which included: standardized design (prospective, randomized, sham controlled with the same primary endpoint at 2 months), use of the same renal denervation technology and technique, consistent study monitoring and data collection (i.e. standard instruction and data collection regarding medications, blinded clinician follow-up, blinded core lab for Ambulatory Blood Pressure Monitoring (ABPM)).

3.1 Randomization

Randomization was established by each individual study. For the purpose of the pooled analysis the original randomization assignment from each study will be respected.

3.2 Blinding

All studies were sham-controlled studies with blinding of the patients and the clinical assessors. Blinding plans were established in each protocol. All ABPM data were analyzed by an independent core lab blinded to treatment assignment.

4 Sample Size Determination

The sample size of each study was independently and prospectively defined for each study. The sample size for the pooled analysis is constrained by the sample sizes in each associated study.

5 Statistical Analyses

5.1 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 9.4 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required.

All p-values and confidence intervals will be nominal without adjustment for multiple comparisons.

5.1.1 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.

5.1.2 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) of the original trial.

5.2 Analysis Populations

The Intent-to-Treat (ITT) population will consist of all randomized subjects analyzed according to their original randomization assignment. Missing data will be handled as per Section 5.5.1.1. This will be the basis of the primary analysis.

The complete Ambulatory Blood Pressure (CA) population will consist of all randomized subjects analyzed according to their original randomization assignment that have ambulatory blood pressure (ABP) values at both baseline and follow-up.

The Per-Protocol (PP) population will include all subjects who are randomized, have treatment delivered successfully (defined as at least two emissions bilaterally) and are free from major issues which may affect the assessment of the treatment:

- Baseline daytime ABP <135/85 mmHg or failure to obtain baseline ABP recording
- Renal artery anatomical exclusion deviations
- Failure to obtain 2-month follow-up ABP recording
- Subjects restarting antihypertensive medication, for any reason, prior to the 2-month primary endpoint.

5.3 Subject Disposition

The number of subjects in each study will be presented along with an accounting of subject disposition. Subject accountability will be summarized by visit. The number of subjects who are enrolled, eligible for follow-up, and number completing clinical follow-up will be summarized for each protocol-required visit. In addition, the number of subjects who complete the study or exit early will be summarized by reason.

5.4 Demographics and Baseline Characteristics

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

5.5 Analysis of Study Endpoints

5.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the change from baseline in daytime ambulatory systolic blood pressure (BP) at 2 months post-procedure.

5.5.1.1 Primary Analysis

Inference will focus on the comparison of the primary efficacy endpoint between the randomized treatment and sham-controlled subjects.

Analysis will be based on a linear model for the change in daytime ambulatory systolic BP at 2 months post-procedure with fixed effects terms for the following covariates: baseline daytime ambulatory systolic BP, randomized study group (i.e. treatment vs. sham), and study (SOLO, TRIO, or RADIANCE II). A fixed effects approach will be used due to the limited number of studies. Estimation will be based on maximum likelihood. The p-value for the randomized study group term and corresponding two-sided 95% confidence interval will be summarized.

For patients that met the defined "High BP Action" changes in each protocol, the last blood pressure measurement prior to the medication change (i.e. the baseline value for ABPM and baseline or 1M for home and office BP) will be used for the reduction in blood pressure in the analysis, as was indicated in the original study designs.

For any subsequent patients with missing 2-month follow-up BP values, multiple imputation will be employed, as was done in RADIANCE II. This will be based on a fully conditional specification using the following covariates for the imputation model: age, sex, and baseline systolic BP. Imputation will be performed separately by randomized treatment group and by study. If necessary, an augmented likelihood approach will be used to facilitate implementation of the imputation model. Twenty imputed data sets will be produced and combined via Rubin's rules[1] to produce the p-value for the primary efficacy endpoint test and the confidence interval for the treatment effect.

The linear model assumes a normal distribution of residuals. A Shapiro-Wilk test for normality will be performed at the 0.05 alpha level based on observed data. If there is significant evidence of non-normality, analysis will be based on ranking the observations (with no imputation) based on (Quade (1967), "Rank Analysis of Covariance", Journal of the American Statistical Association, Vol 62, No 320).

[1] Rubin, D. B. (1976). "Inference and Missing Data." Biometrika 63:581–592.

5.5.1.2 Sensitivity Analysis

A tipping point sensitivity analysis for missing data will be performed. The tipping point analysis will evaluate best case, worst case, and multiple cases in-between. A subject with missing data will be imputed from a range of that subject's study-specific treatment group BP reduction percentile value: 0% (minimum), 25%, 50%, 75%, 100% (maximum). This will result in a 5x5 table with active treatment on one side and control on the other. Within each cell of the 5x5 table the endpoint results will be calculated, and consistency will be evaluated.

Analysis of the primary endpoint will be repeated for the CA and PP populations.

5.5.2 Secondary Endpoints

The following secondary endpoints will be analyzed, using a similar methodology as that for the primary endpoint, including the handling of missing data for the ITT population. Analysis will be based on the ITT, CA, and PP populations.

- Reduction in average 24-hr ambulatory systolic BP at 2 months post procedure
- Reduction in average home systolic BP at 2 months post procedure
- Reduction in average office systolic BP at 2 months post procedure
- Reduction in average nighttime systolic BP at 2 months post procedure
- Reduction in average daytime ambulatory diastolic BP at 2 months post procedure
- Reduction in average 24-hr ambulatory diastolic BP at 2 months post procedure
- Reduction in average home diastolic BP at 2 months post procedure
- Reduction in average office diastolic BP at 2 months post procedure
- Reduction in average nighttime diastolic BP at 2 months post procedure

5.6 Heterogeneity/Poolability Analyses

Given the limited number of studies, study will be included as a fixed covariate in the primary analysis. A sensitivity analysis that includes an interaction term for study and treatment group will also be performed.

Standard meta-analysis summaries and forest plots will be produced. Generally, a one-stage individual patient data meta-analysis approach will be used to obtain estimates of the pooled treatment effect. A two-stage approach will be used to obtain further statistics and forest plots.[2]

5.7 Safety Analyses

Pooled safety analyses for the studies are outlined in the RADIANCE-II SAP. Major adverse events will be reported through 30 days including stenosis through 2 months at time of 2-month analysis and through 6 months at time of 6-month analysis.

The following are considered Major Adverse Events (MAE);

The 30-day post randomization incidence of:

- All-cause mortality
- New onset (acute) end-stage renal disease (eGFR <15 mL/min/m^2 or need for renal replacement therapy)
- Significant embolic event resulting in end-organ damage (e.g., kidney/bowel infarct, lower extremity ulceration or gangrene, or doubling of serum creatinine)
- Renal artery perforation requiring an invasive intervention
- Renal artery dissection requiring an invasive intervention
- Major vascular complications (e.g., clinically significant groin hematoma, arteriovenous fistula, pseudoaneurysm) requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion (requiring more than 2 units of packed red blood cells within any 24-hr period during the first 7 days post randomization)
- Hospitalization for hypertensive or hypotensive crisis
- Hospitalization for major cardiovascular- or hemodynamic- related events (e.g. HF; MI; Stroke)
- New onset stroke
- New onset myocardial infarction

And,

- The 6-month post-randomization incidence of new renal artery stenosis >70%, confirmed by CT or MR angiography.

[2] https://training.cochrane.org/handbook/current/chapter-26#section-26-4, accessed 11July2022.

5.8 Subgroup Analyses

Subgroup analysis of the will be performed for the following subgroups defined by baseline characteristics:

- Sex
- Race (Black versus non-black)
- Age
- Baseline ambulatory daytime systolic BP
- Baseline ambulatory nighttime systolic BP
- Baseline home systolic BP
- Baseline office systolic BP
- 24 hour ambulatory pulse pressure
- Baseline 24-hour ABP heart rate
- eGFR (<60 vs. ≥60 ml/min/1.73 m^2)
- Geography: US/Outside of US
- Abdominal obesity split for male >102 cm and ≤102 cm; and for female >88 cm and ≤88 cm
- BMI (<30 vs. ≥30)
- Diabetes (yes/no)
- Number of meds at enrollment
- Orthostatic hypertension defined as office standing minus office seated systolic blood pressure (SBP) ≥ 20mmHg and/or office standing minus office sitting diastolic blood pressure (DBP) ≥ 10mmHg at baseline (yes/no)
- For the RDN group only: Number of ablations, untreated accessory arteries

These analyses are intended to demonstrate consistency of results across subgroups. Covariates will be centered by their mean value to prevent ecological bias[3].

[3] Hua H, Burke DL, Crowther MJ, Ensor J, Tudur Smith C, Riley RD. One-stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and

Subgroup analyses will be performed using the ITT and PP analysis set. For each subgroup, a linear regression model will be fit that includes fixed effects for randomized arm, subgroup, and treatment by subgroup interaction. For each subgroup analysis, the p-value for the treatment by subgroup interaction will be presented. Additionally, at each level of the subgroup of interest, the within group estimates will be summarized.

5.9 Multivariable Analysis

A multiple linear regression analysis on the per-protocol population to assess the predictive variables of the changes in daytime ambulatory systolic blood pressure will be conducted. For the analysis, the dependent variable will be the change in daytime SBP from baseline to 2-months, and the independent variables will include:

- Group (Denervation =1, sham = 0)
- Study
- Sex
- Race (Black versus non-black)
- Age
- Baseline ambulatory daytime systolic BP
- Baseline 24 hour ABP heart rate
- eGFR
- Geography
- Abdominal obesity split for male >102cm and ≤102cm; and for female >88cm and ≤88cm

5.10 Observational Analyses

Additional observational assessments of effectiveness will be evaluated including but not limited to between-group differences and within-group changes.

across-trial information. Stat Med. 2017 Feb 28;36(5):772-789. doi: 10.1002/sim.7171. Epub 2016 Dec 1. PMID: 27910122; PMCID: PMC5299543.

5.10.1 Analyses at 2 months

- Change in Home BP and Office BP from Baseline to 2 months (including 1 month)
- Percentage of subjects who are controlled in the absence of added antihypertensive medication in each arm at 2 months post procedure (daytime ABP <135/85 mmHg; 24-hr ABP< 130/80 mmHg; office BP <140/90 mmHg; home <135/85 mmHg)
- Percentage of subjects who are controlled at 2 months post procedure (daytime ABP <135/85 mmHg; 24-hr ABP< 130/80 mmHg; office BP <140/90 mmHg; home <135/85 mmHg)
- Incidence of ambulatory systolic BP (daytime/24-hr/night-time) reductions of ≥5 mmHg, ≥10 mmHg, ≥15 mmHg, and ≥20 mmHg at 2 months post procedure
- Incidence of home systolic BP reductions of ≥5 mmHg, ≥10 mmHg, ≥15 mmHg, and ≥20 mmHg at 2 months post procedure
- % patients needing addition of antihypertensive medications prior to the 2 month endpoint
- Analysis of change in blood pressure at 2 months (control rates and level of BP reduction) as function of baseline BP quantiles
- Reduction in heart rate at 2 months post procedure (office, 24-hour, daytime, and nighttime heart rate)

5.10.2 Analyses at 6 months

All analyses at 6 months will be based on evaluable data. Analyses at 6 months are planned, but not limited to:

- The aforementioned primary and secondary endpoints including adjustment for medication burden as well, as medication burden will also be evaluated at 6 months post procedure.
- The aforementioned observational analyses at 2 months will also be evaluated at 6 months post procedure. However, the change in blood pressure over time will include all visits between baseline and 6 months (1, 2, 3, 4, and 5 months)
- Change in ABP from Baseline to 6 months (including 2 months)
- Time in target range (of control) from baseline to 6 months in blood pressure (daytime ambulatory, 24-hour ambulatory, and home)
- Visit-to-visit variability of BP excluding Baseline for visits at 2 months to 6 months as calculated via the various methods outlined in publication by Hussein et al.[4]

5.11 Interim Analyses

Analysis of data will be based on a single analysis pooling each study based on the final analysis data set for the 2-month endpoint for each respective study. There was no interim analysis performed for the purposes of early stopping or study modifications for any of the individual studies.

5.12 Protocol Deviations

Protocol deviations will not be summarized as part of this analysis.

6 Changes from Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.