STATISTICAL ANALYSIS PLAN SUMMARY

TITLE:	A Post-Market Study of Transcatheter Perivascular Renal Denervation for the Treatment of Hypertension using the Ablative Solutions Inc. Peregrine System™ Infusion Catheter
SHORT TITLE:	The Peregrine Post-Market Study
PROTOCOL ID:	CR0001
INVESTIGATIONAL PRODUCT:	Peregrine System™ Infusion Catheter
INDICATION:	Hypertension
ClinicalTrials.gov ID:	NCT02570113
PHASE:	Post market clinical follow up study
SPONSOR:	Ablative Solutions, Inc. 6203 San Ignacio Avenue, Suite 110 San Jose, CA 95119, US
COORDINATING INVESTIGATORS:	Prof. Dr. med. Horst Sievert
SAP VERSION:	Final 2.0
DATE:	28 October 2018

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ENDPOINTS AND STATISTICAL ANALYSIS

Sample Size Calculation

The study is not powered for formal hypothesis testing.

The primary safety endpoint is defined by the absence of any of the following events as adjudicated by the CEC through 1-month post procedure:

1. Peri-procedural major vascular complications
2. Major Bleeding as defined by the thrombolysis in myocardial infarction (TIMI) Bleeding Classification
3. Acute Kidney Injury (AKI) within 1 month of the procedure
4. Peri-procedural death (within 1 month of the procedure)

With a sample size of 60 evaluable subjects for the primary safety endpoint which is expected to vary between 85% and 100%, the associated width of the 95% 2-sided exact binomial confidence intervals range from 19.5% to 6.0%, respectively. This accuracy was deemed satisfactory and sufficient to fulfill the study objectives and to provide relevant information to design appropriately a larger study.

The primary performance endpoint is defined as a reduction of 24-hour mean ambulatory systolic blood pressure following treatment at 6 months, as compared to baseline. Assuming 10% of subjects will not participate in the performance evaluation at 6-months (death, drop-out, loss-to-follow-up, withdrawal), then with a sample size of 54 evaluable subjects and results on primary performance endpoint expected to vary between 85% and 100%, the associated width of the 95% 2-sided exact binomial confidence intervals range from 20.5% to 6.6%, respectively. This accuracy was deemed satisfactory and sufficient to fulfill the study objectives and to provide relevant information to design appropriately a larger study.

Endpoints and Planned Statistical Analysis

The following populations are defined for analysis:

- Full Analysis Set (FAS): The full analysis set contains all consented and treated subjects
- Per-protocol (PP): The per-protocol analysis set consists of all subjects treated with the study dose (0.6 mL dehydrated alcohol) and with no major protocol deviations. If any subjects meet these criteria for removal from the full analysis set, then all endpoint analyses will be additionally conducted in this subset of subjects. These analyses will be considered supplementary

All analyses will be conducted using the FAS unless otherwise specified. The FAS will be the primary analysis set for all statistical analyses

Primary Safety Endpoint

The primary safety endpoint is defined as the absence of any of the following events as adjudicated by the Clinical Events Committee (CEC) through 1-month post procedure:

1. Peri-procedural major vascular complications
2. Major Bleeding as defined by the TIMI Bleeding Classification
3. Acute Kidney Injury (AKI) within 1 month of the procedure
4. Peri-procedural death (within 1 month of the procedure)

Primary Performance Endpoint

The primary performance endpoint is defined as any reduction of 24-hour mean ambulatory systolic blood pressure following treatment at 6 months, as compared to baseline.

Secondary Safety Endpoints

Secondary safety endpoints include:

1. Proportion of subjects with a decline in estimated glomerular filtration rate (eGFR) by >25% from baseline to 6-month follow-up;
2. Change in serum creatinine from baseline to 6-month follow-up
3. New renal arterial stenosis > 60% from the baseline at the 6-month follow-up, to be confirmed by the same imaging method used at baseline.
4. Stroke or transient ischemic attack (TIA) within 1 month of the procedure
5. Myocardial Infarction (MI) within 1 month of the procedure
6. Major Adverse Events (MAEs) through 6-month post-procedure.

Adverse events will be recorded at each of the follow-up periods. Severity, device relatedness, and sequelae of each adverse event will be recorded.

Secondary Performance Endpoints

Secondary performance endpoints include the following:

1. Changes in antihypertensive medications at 7 days, 1-, 3-, 6- and 12-months post-procedure
2. Changes in systolic and diastolic clinic/office blood pressure following treatment compared to baseline, assessed at 7 days, 1-, 3-, 6- and 12-months post-procedure

3. Changes in systolic and diastolic 24-hour mean daytime and nighttime ambulatory blood pressure, assessed at 1-, 3-, 6- and 12-months post-procedure
4. Changes in systolic 24-hour mean ambulatory blood pressure assessed at 1-, 3- and 12-months post-procedure
5. Changes in diastolic 24-hour mean ambulatory blood pressure assessed at 1-, 3-, 6- and 12-months post-procedure
6. Change in eGFR from baseline, to evaluate the progression of Chronic Kidney Disease (CKD) after 1, 3, 6 and 12 months
7. The progression of kidney disease in subjects with ≤60 mL/min/1.73m^2 will be evaluated by comparing the change in eGFR during the study to the historical loss (reduction) of eGFR during the 3 years prior to renal denervation for each individual subject
8. Change in albuminuria from baseline to 3 months post-procedure, with additional assessments at each study time point
9. Change in albuminuria categorization from baseline to 3 months post-procedure, with additional assessments at each study time point
10. Change in serum creatinine and cystatin-C from baseline to 3 months post-procedure, with additional assessments at each study time point

General Considerations

- Continuous variables will be summarized using standard quantitative statistics: number of non-missing observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations, if any, will also be summarized. Categorical variables will be summarized using classical frequency statistics: number of non-missing observations and percentages by categories. Number and percent of missing data, if any, will also be summarized.
- For all success/failure endpoints (including but not limited to primary safety endpoint), the 95% 2-sided exact binomial confidence intervals will be presented.
- Demographics, medical history and procedural characteristics will be summarized as noted above.
- For each variable, the baseline value will be defined as the last value collected before the procedure.
- There will be no formal hypothesis testing conducted in the study. Ninety-five percent confidence intervals, when presented, are intended to be descriptive in nature only. For binary variables, confidence intervals will be calculated via exact binomial methods. For continuous variables, the confidence interval of the mean will be constructed using the normal approximation.
- Unless otherwise noted, only complete data will be reported and no imputation for missing values will be conducted. Sensitivity analyses will be conducted for the primary safety and efficacy endpoints whereby missing data will be imputed using multiple imputation and LOCF methods.