STATISTICAL ANALYSIS PLAN
The TARGET BP OFF-MED Trial

A Phase 2, Multicenter, Blinded, Sham Procedure-Controlled Trial of Renal Denervation by the Peregrine System Kit, in Subjects with Hypertension, in the Absence of Antihypertensive Medications

Sponsor:	Ablative Solutions, Inc. 301 Edgewater Place Suite 100 Wakefield, MA 01880
Indication:	Hypertension
Protocol ID:	CR0014 v6.0 01 July 2020
Document Date:	19 November 2021
Document Version:	4.0

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
AE	adverse event
ANCOVA	analysis of covariance
ASI	Ablative Solutions, Inc.
BP	blood pressure
COVID-19	coronavirus disease of 2019
CRF	Case Report Form
CTA	computed tomography angiography
CVA	cerebrovascular accident
DSMB	Data Safety Monitoring Board
DDD	defined daily dose
DUS	duplex ultrasound
ECG	electrocardiogram
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ITT	Intent-to-Treat
MAE	major adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRA	magnetic resonance angiography
NYHA	New York Heart Association
PP	Per Protocol
PT	Preferred Term
SAP	statistical analysis plan
SAE	serious adverse event
SOC	System Organ Class
TEAE	treatment emergent adverse event
UADE	unanticipated adverse device effect
WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) in conjunction with the table shells is intended to prospectively (a priori) outline the analyses and presentations of data that will form the basis for conclusions to be reached to answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in clinical trials. Results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report for this study. This plan is based on Version 6.0 of the study protocol dated 01 July 2020.

3. INVESTIGATIONAL PLAN

3.1. Study Objective

The primary objective of this proof-of-concept study is to evaluate the efficacy of renal denervation by alcohol-mediated neurolysis using the Peregrine System™ Kit (also referred to as Peregrine Kit) in hypertensive subjects, when used in the absence of antihypertensive medications, as evaluated by change in mean 24-hour ambulatory systolic blood pressure (SBP) from baseline to 8 weeks post-treatment.

Secondary objectives are to evaluate the acute and chronic safety of renal denervation by alcohol-mediated neurolysis using the Peregrine Kit in hypertensive subjects, up to 2 years post-treatment and to evaluate the efficacy of renal denervation by alcohol-mediated neurolysis using the Peregrine Kit on blood pressure in hypertensive subjects, up to 1 year post-treatment.

3.2. Overall Study Design and Plan

This is a Phase 2, prospective, randomized, blinded, sham procedure-controlled, multicenter trial to assess the efficacy and safety of renal denervation by alcohol-mediated neurolysis using the Peregrine Kit. Subjects with a documented history of uncontrolled hypertension who are taking 0, 1, or 2 antihypertensive medications at enrollment will be recruited. Following screening, eligible subjects will enter a 4-week run in period during which they will take no antihypertensive medications.

Subjects who continue to be eligible at the end of the run-in period will be randomized in a 1:1 ratio to one of the following 2 groups via central randomization (stratified by study site):

- Treatment Arm: renal denervation (using the Peregrine Kit) performed with alcohol (0.6 mL per treated renal artery) infused through the Peregrine Catheter (minimum treatment: the 2 main renal arteries [1 per side]; physician is also permitted to treat up to 1 additional accessory artery on each side. Thus, the planned maximum total dose of alcohol is 4 x 0.6 mL = 2.4 mL.)
- Sham Control Arm: only renal angiography will be performed. No renal denervation and no alcohol infusion will be performed.

Subjects will be discharged from the study site the day after the procedure if there are no safety concerns, per the physician's judgment. Subjects with an estimated glomerular filtration rate (eGFR) of >45 and <60 mL/min/1.73 m^2 will return to provide a blood sample for measurement of serum creatinine 48 to 96 hours after the procedure. Subjects will continue to take no antihypertensive medications during the first 8 weeks after the procedure (except for emergencies, as defined in the protocol). After 8 weeks, antihypertensive medications are permitted according to the protocol-defined criteria and proposed titration scheme.

Follow-up visits will be performed at 4 weeks, 8 weeks, 3 months, 6 months, 1 year, and 2 years, as well as telephone contacts at 2 and 6 weeks in Ireland only.

The study will be unblinded after the last subject has completed the 6-month visit.

Crossover from the Sham Control Arm to the Treatment Arm may be allowed, at the discretion of the treating investigator, after the Data Safety Monitoring Board (DSMB) has reviewed the 6-month data from all subjects, the study has been unblinded, and the subject has completed the 1-year follow-up visit.

A subject is considered enrolled once he/she signs the informed consent form. All enrolled subjects will then proceed to complete the screening and baseline tests. If they do not meet the study criteria, they will be withdrawn from the study (status Screen Failure) and will not count towards the treated study population.

3.2.1. Blinding

The subject, sponsor, and hypertensionist/nephrologist performing the screening and follow-up assessments are blinded. The interventionalist and cath lab staff are unblinded. Details of study blinding are contained in the study Randomization and Blinding Plan.

3.3. Description of Study Hypotheses

This study is designed as a proof-of-concept study. It is therefore not formally powered for the primary endpoint. The purpose of the trial is to determine if there is an adequate treatment effect to proceed to a pivotal study. It is planned to randomize approximately 90 subjects (45 per group) to achieve 80 evaluable subjects (for the primary efficacy endpoint analysis).

Primary Efficacy Endpoint

The primary efficacy endpoint of the change in mean 24-hour ambulatory SBP at 8 weeks post-treatment will be compared between the 2 treatment groups.

The following table provides examples of observed treatment effects and standard deviations (SDs) that would be considered statistically significant at alpha = 0.05, for the change in mean 24-hour ambulatory SBP at 8 weeks post-treatment with 80 evaluable subjects:

Treatment Difference	Standard Deviation
3.5 mmHg	8 mmHg
4.4 mmHg	10 mmHg
5.3 mmHg	12 mmHg

A study of the planned size would be powered at 80% to detect a difference between intervention and control of 5.1 mmHg assuming a SD of 8 mmHg in each group and two-sided alpha of 0.05 using the independent two-sample t-test. A difference between treatment and control of 5 mmHg is considered clinically meaningful and consistent with previous trials of renal denervation in a similar population (Townsend et al. 2017). An observed difference between groups of 5 mmHg with an observed SD as high as 11.2 mmHg per group would be considered statistically significant at a two-sided alpha level of 0.05.

3.4. Study Endpoints

3.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the change in mean 24-hour ambulatory SBP from baseline to 8 weeks post-treatment. This will be summarized and compared between the 2 treatment groups using the independent two-sample t-test.

3.4.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Change in mean 24-hour ambulatory diastolic blood pressure (DBP) from baseline to 8 weeks
- Change in mean 24-hour ambulatory SBP and DBP from baseline to 6 months and 1 year
- Change in mean daytime (07:00 to 21:59) ambulatory SBP and DBP from baseline to 8 weeks, 6 months, and 1 year
- Change in mean nighttime (22:00 to 6:59) ambulatory SBP and DBP from baseline to 8 weeks, 6 months, and 1 year
- Change in mean office SBP and DBP from baseline to 8 weeks, 6 months, 1 year, and 2 years
- Percentage of subjects controlled to target blood pressure values.
- Use of antihypertensive medication(s) from time of procedure to 8 weeks post-treatment (emergency use medication).
- Use of antihypertensive medication(s) (including increases/decreases) from 8 weeks to 6 months post-treatment (titrated according to standardized formula to maintain a target office SBP of <140 mmHg and ≥90 mmHg, see Section 7.2.2 of the protocol for more detail regarding medication titration).
- Compliance with not taking antihypertensive medications, as assessed by blood and urine testing, through 8 weeks post-treatment.

3.4.3. Secondary Safety Endpoints

Secondary safety endpoints include:

- Major adverse events (MAEs) through 30 days post-treatment, as adjudicated by the Clinical Events Committee (CEC). A MAE is defined as any of the following:
  - All-cause death
  - End-stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m^2 or need for renal replacement therapy)
  - Significant embolic event resulting in end-organ damage or requiring intervention to prevent it
  - Major vascular complications, including major renal artery dissection, renal artery aneurysm or pseudoaneurysm that required intervention or led to renal artery stenosis (>60% diameter stenosis)
  - Major bleeding related to renal denervation within the renal arteries, or related to the Peregrine Catheter when in the body (per protocol bleeding definition)
  - Significant acute (post-procedural) renal artery stenosis (>60% diameter stenosis) as indicated by the renal angiogram post renal denervation, and confirmed by the angiography core laboratory, which led to one of the following: (i) acute kidney injury per modified Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) definition, as confirmed by renal function blood test, or (ii) percutaneous intervention.
  - Hypertensive crisis (hypertensive emergency only)

  - Hypotensive crisis
  - Symptomatic hypotension that required a change in antihypertensive medications, or medications to increase blood pressure (e.g., persistent syncope, lightheadedness)
- Changes in eGFR from baseline to 8 weeks and 6 months post-treatment.
- Decreases in eGFR >25% from baseline to 8 weeks and 6 months post-treatment.
- Rate of adverse events (AEs) (serious and non-serious), peri-procedurally, at discharge, and at each of the follow-up time points.
- Device success (defined as the ability to insert the Peregrine Catheter into the lumen of the renal artery [target vessel], deploy the guide tubes inside the renal artery, deploy the needles through the arterial wall, deliver the intended dose of alcohol, retract the needles and the guide tubes back in the catheter, and remove the catheter from the access site without any related complications or events)
- Procedure success (defined as device success with freedom from peri-procedural MAEs).

Adverse events will be recorded from the time of signing the informed consent form through the end of study participation. Date of report; date of onset; whether the AE is serious or not; whether the AE is considered an MAE; whether the AE is considered a serious adverse device effect (SADE); whether the AE is considered a suspected unexpected adverse drug reaction; causal relationship (to Peregrine Catheter, study drug [alcohol], and study procedure, separately); action taken; outcome; date recovered/resolved; and date of death (if applicable) of each adverse event will be recorded.

4. PATIENT POPULATIONS

4.1. Data Sets to be Analyzed

The Intent-to-Treat (ITT) Analysis Set will include all subjects who were randomized regardless of whether treatment was received. Subjects will be analyzed according to their randomized treatment group, irrespective of treatment received.

The Safety Analysis Set will include all subjects who received treatment. Subjects will be analyzed according to the actual treatment received, irrespective of treatment assignment.

The Per-Protocol (PP) Analysis Set will include subjects with no important protocol deviations. Subjects will be analyzed according to the actual treatment received. Important protocol deviations include:

- Not meeting inclusion/exclusion criteria
- Not receiving bi-lateral treatment or an unsuccessful procedure
- Receiving anti-hypertensive treatment prior to evaluation of the primary ambulatory blood pressure monitoring (ABPM) measurement
- Not completing the primary ABPM measurement

All deviations will be reviewed prior to unblinding to assess if additional exclusions will be applied.

Unless otherwise noted, the ITT and PP Analysis Sets will be used for all efficacy analyses and safety analyses will be conducted in the Safety Analysis Set.

4.2. Protocol Deviations

This study will be conducted as described in the protocol, except for an emergency situation in which the protection, safety, and well-being of the patient require immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). All protocol deviations will be documented on the protocol specific deviation form of the eCRF. All protocol deviations will be summarized. Those protocol deviations associated with COVID-19 will be additionally summarized separately as indicated by the site and checked on the eCRF.

5. STATISTICAL METHODS

5.1. Determination of Sample Size

The study is not powered for formal hypothesis testing.

5.2. General Considerations

5.2.1. General Methods

Two unblinded team members (either two statisticians or a statistician and a statistical programmer) will be assigned for all analyses. This will allow for discussion of output and direct QC of statistical programming on the exact same dataset.

In general, continuous variables will be summarized with descriptive statistics (n, mean, SD, range, median, and interquartile range). The difference between groups will be presented and the normal approximation will be used to calculate two-sided 95% confidence intervals (CIs). Change from baseline, when relevant, will be computed as the paired mean difference and 95% CI of the mean difference at each time point.

For all continuous primary and secondary blood pressure endpoints, changes over time will be additionally explored in mixed effects repeated measures analyses, including the values at all time points.

Categorical variables will be summarized as frequencies and percentages. Relative risks and 95% CIs will be computed.

All statistical analyses will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, NC 27513, USA).

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 CIs, when presented, are intended to be descriptive in nature only. For binary variables, CIs will be calculated via exact binomial methods. For continuous variables, the CI of the mean will be constructed using the normal approximation.

5.2.2. Adjustments for Covariates

Analysis of changes in blood pressure measures will be adjusted for baseline values using analysis of covariance (ANCOVA). Raw mean values will be presented, however, comparisons between groups will include the baseline value of the associated measure as described below. There is no other planned adjustment for covariates.

5.2.3. Handling of Dropouts or Missing Data

For the primary efficacy endpoint analysis, all available data will be used. As additional analyses, patients who meet the protocol defined criteria for antihypertensive drug treatment within the 8 weeks prior to assessment of the primary endpoint will be assigned their baseline value of ABPM at 8 weeks. Additional sensitivity analyses will be conducted removing those

subjects who receive antihypertensive treatment within 8 weeks. Also, as a secondary sensitivity analysis, missing data will be imputed via multiple imputation techniques.

There will be no imputation of data for secondary efficacy endpoints or other endpoints; only available data will be used, with the exception of analyses at 8 weeks for subjects receiving protocol defined antihypertensive therapy within 8 weeks. Analyses will be conducted with all available data and only in subjects who did not receive antihypertensive treatment between baseline and 8 weeks.

This study allows for cross-over of control subjects once the participant has passed the 1-year study visit. Subjects who cross-over will be considered withdrawn from the main study as of the day of their cross-over procedure and will no longer be analyzed with the main study cohort (i.e., their data will be missing for any subsequent scheduled study visits).

5.2.4. Interim Analyses and Data Monitoring

There are 2 planned interim analyses: a blinded 8-week interim analysis (conducted after all subjects have completed the 8-week visit), and an unblinded 6-month interim analysis (conducted after all subjects have completed the 6-month visit and the study has been unblinded).

Neither of the planned interim analyses for this study is intended to be assessed with the purpose of altering the study design or sample size.

The 8-week interim analysis will include available data through the 8-week assessment including, but not limited to, primary efficacy and safety data. The individual treatment assignments will remain blinded at this time. The 8-week interim analysis will be assessed by the unblinded DSMB in accordance with the DSMB charter. Analysis will be conducted by the independent unblinded DSMB statistician. Only aggregate data, by treatment group, will be provided outside of the DSMB. Data will be cleaned to the extent possible but not locked for this analysis. All outstanding adjudications for events occurring with 8-weeks should be resolved. A separate interim analysis plan will provide additional details as to the content and dissemination of these results.

The 6-month interim analysis will include all available data through 6 months. The study will be unblinded for analysis at this time. The 6-month interim analysis results will help inform the appropriateness of the crossover.

5.2.5. Multicenter Studies

Consistency of the primary efficacy endpoint across study sites (centers) will be examined. Results will be presented by study site. There will be insufficient power to determine differences between sites, however, any notable differences between sites will be explored. Sites with less than 10 subjects may be combined by country in order to assess if there are statistical differences between sites. The interaction p-value from the ANOVA model for treatment by site will be calculated. A p-value < 0.15 will be viewed as evidence of differences between sites and will be discussed in the final study report.

Additionally, regions (US and Europe) will be pooled for the analysis by treatment group. Consistency of the effects by region will be explored by displaying the primary efficacy results by region. The interaction term for region by treatment will be calculated using analysis of variance. A treatment by region interaction p-value less than 0.15 will be explored further and described in the final study report.

5.2.6. Multiple Comparisons/Multiplicity

There is no formal hypothesis testing and thus no adjustment for alpha in necessary. In addition, there is a single primary endpoint in this study. Analyses of secondary endpoints are considered supportive. As such, there is no adjustment to alpha for multiplicity necessary to control Type I error.

5.2.7. Examination of Subgroups

The following subgroups will be presented for the primary efficacy endpoint in the ITT analysis set:

- Age grouped according to the median age
- Gender (male vs. female)
- Region (US vs Europe)
- Ethnicity (US only)
- Race (US only)
- Country
- Subjects who require a change of antihypertensive drugs during the post-procedure follow-up period
- Subjects with baseline ambulatory SBP >140 mmHg and DBP <90 mmHg versus all other subjects
- Subjects with baseline eGFR within the following groupings 45-60, 61-75, and >75 mL/min/1.73 m^2. Comparison of changes in eGFR will also be explored within this subgroup.

The following subgroup will be presented for the secondary efficacy endpoints in the ITT Analysis Set:

- Subjects with baseline daytime ambulatory SBP >140 mmHg and DBP <90 mmHg versus all other subjects.

5.2.8. Analysis Windows and Definitions

The following visit windows were defined per protocol for follow-up:

Week -1 (- 7 days)	**Week 4 (28 days)**	**Week 8 (56 days)**	**Month 3 (90 days)**	**Month 6 (180 days)**	**Year 1 and 2 (365 and 730 days)**
± 2 days	**± 7 days**	**± 7 days**	**± 2 weeks (14 days)**	**± 4 weeks (28 days)**	**± 8 weeks (56 days)**

For the day of the procedure (Day 0), flexibility in scheduling is permitted (up to 1 week), e.g., due to cath lab availability, based on physician discretion and with careful consideration of subject safety, thus data collected at the Week -1 visit will be acceptable if the day of procedure is extended by 1 week such that values up to 16 days (14+2 days) prior to procedure will be considered valid reading for analysis of baseline measures. If multiple baseline values are present prior to procedure, the valid reading that is closest to the day of procedure within window will be used.

For the purposes of statistical analysis, the 8-week window will be extended to -15 and +30 days (i.e., the window for valid data will range from 41 to 86 days) allowing blood pressure measures collected within a reasonable time frame but beyond the protocol defined window to be analyzed, provided that the subject remains off antihypertensive medication prior to the visit assessments at 8 weeks.

A table summarizing visit compliance will be included as part of the overall subject disposition.

5.3. Patient Disposition, Demographics and Other Baseline Characteristics

A tabulation of patient disposition will be presented including number treated, number completing each visit and number of withdrawals and lost to follow-up, including primary reason for withdrawal as documented on the case report form.

Baseline demographics and medical history will be summarized for the ITT, PP and Safety analysis sets.

5.3.1. Listing of Individual Data

A by-patient listing of key demographic data and medical history will be presented.

5.4. Primary Endpoints

The primary efficacy endpoint will be summarized in the ITT analysis set and the PP analysis set (if it differs from ITT). For the primary efficacy endpoint analysis, the primary population for analysis is ITT, while the PP population is considered supportive (for sensitivity analyses).

5.4.1. Primary Efficacy Endpoint

The mean change in 24-hour ambulatory SBP from baseline to 8 weeks post-treatment will be presented in each group. The difference between groups will be summarized and compared using ANCOVA with adjustment for the baseline 24-hour ambulatory SBP.

The protocol defined window for the 8-week (56 day) visit is ±7 days. For the purposes of analysis, measurements obtained within -15 days or +30 days (i.e., between 41 and 86 days) will be considered valid and will be analyzed as part of the primary endpoint analysis, provided that the subject remained off antihypertensive medication prior to collection of ABPM.

For the primary analysis, all available data will be used. There will be no imputation of data at 8 weeks. This analysis will be repeated in the PP analysis set.

In addition to the primary analysis, the following secondary and sensitivity analyses will be conducted:

1. Subjects who meet the protocol defined criteria for antihypertensive drug treatment and receive treatment within the 8 weeks prior to assessment of the primary endpoint will have their 8-week value imputed with their baseline value of ABPM.

2. Subjects who meet the protocol defined criteria for antihypertensive drug treatment and receive treatment within 8 weeks will be removed from the analysis.

3. Subjects who receive antihypertensive treatment within 8 weeks for any reason or in whom antihypertensive medications are detected via compliance samples will be removed from the analysis.

4. Missing data at 8 weeks will be imputed via multiple imputation techniques. The following covariates will be considered for the imputation: treatment group, age, gender, history of diabetes, BMI, anatomy defined by length from ostium to bifurcation, number of medications at baseline, baseline office systolic pressure, 8-week office systolic pressure, baseline 24-hour ambulatory SBP. These factors were chosen based on clinical experience and recent literature (Fengler, 2016) (Id, 2016) (Kandzari, 2015).

5. Missing data at 8 weeks and data for those subjects who meet the protocol defined criteria for antihypertensive drug treatment and receive treatment within 8 weeks will be imputed via multiple imputation techniques.

An additional exploratory analysis will be conducted, which combines the treatment failures (subjects receiving rescue medication) with the continuous 24-hour ambulatory SBP measurement in a hierarchical fashion using the approach described in Finkelstein and Schoenfeld (1999) and later adapted to the Win Ratio by Pocock (2012). Using this approach, each subject is compared to every other subject first as to whether or not the subject received rescue medication. If both subjects did or did not receive rescue medication (i.e., there is a tie), then the subjects will have their change in 24-hour ambulatory SBP at 8 weeks compared. A score of -1 will be assigned to a loss and a score of +1 will be assigned to a win. For example:

- If Subject A receives rescue medication within 8 weeks and Subject B does not, Subject A loses (score -1), and Subject B wins (score +1)
- If neither receive rescue medication within 8 weeks, then if Subject A has a larger reduction in 24-hour ambulatory SBP at 8 weeks compared to Subject B, then Subject A wins (score +1) and Subject B loses (score -1).

After all between-subject comparisons have been performed, scores will be summed to obtain a cumulative score for each subject, and the scores between treatment groups will be compared using the Mann-Whitney U test. The resulting p-value will be presented. The win ratio will also be presented. It is calculated as number of "wins" divided by the number of losses out of all comparisons of intervention to sham subjects.

5.5. Secondary Endpoints

In general, all secondary efficacy endpoints will be summarized in the ITT Analysis Set and the PP Analysis Set (if it differs from ITT). All secondary safety endpoints, with the exception of

Device and Procedure Success, will be summarized in the Safety Analysis Set. Device and Procedure Success will be summarized in the ITT Analysis Set.

5.5.1. Secondary Safety Endpoints

5.5.1.1. MAE within 30 days

The number and percent of subjects experiencing any MAE within 30 days as adjudicated by the clinical events committee will be summarized and two-sided 95% exact CIs will be reported. The difference between groups will be summarized, two-sided 95% exact Cis will be reported and the groups will be compared via the Fisher's Exact test. Only subjects who have experienced an MAE within 30 days or who have at least 21 days of follow-up (includes subjects who have had their 4 weeks visit minus the allowable visit window). These analyses will be conducted in the Safety Analysis Set.

5.5.1.2. Changes in eGFR from Baseline to 8 weeks and 6 months Post-Treatment

The change in eGFR will be summarized between baseline and 8 weeks and baseline and 6 months. Changes in eGFR at 8 weeks and 6 months will be compared between groups using the independent two-sample t-test. These analyses will be conducted in the Safety Analysis Set.

5.5.1.3. Decreases in eGFR >25% from Baseline to 8 weeks and 6 months Post-Treatment

The number and percent of patients with greater than a 25% reduction in eGFR will be summarized at 8 weeks and 6 months. Groups will be compared using Fisher's Exact test. These analyses will be conducted in the Safety Analysis Set.

5.5.1.4. Rate of Adverse Events (Serious and Non-Serious), Peri-Procedurally, at Discharge, and at Each of the Follow-up Time Points.

Coded AEs will be summarized at each follow-up time period (any events occurring prior to and including the follow-up time) and overall according to system organ class (SOC) and Preferred Term (PT) by treatment group as described in Section 5.8.1 below.

5.5.1.5. Device Success

Device success is defined as the ability to insert the Peregrine Catheter into the lumen of the renal artery [target vessel], deploy the guide tubes inside the renal artery, deploy the needles through the arterial wall, deliver the intended dose of alcohol, retract the needles and the guide tubes back in the catheter, and remove the catheter from the access site without any related complications or events. The number and percent of devices used successfully will be summarized in the treated group. Devices opened but not used (i.e. no attempt was made to insert the device into the body) will not be included in the summary. These analyses will be conducted in the ITT analysis set.

5.5.1.6. Procedure Success

Procedure success is defined as device success with freedom from peri-procedural MAEs and will be summarized at the subject level. The number and percent of subjects who experience procedure success will be summarized in the treatment group. These analyses will be conducted in the ITT Analysis Set.

5.5.2. Secondary Efficacy Endpoints

5.5.2.1. Change in Mean 24-hour, Daytime, and Nighttime Ambulatory SBP and DBP from Baseline to Time Points Post-Treatment.

The mean change in ambulatory blood pressures at all collected time points will be reported with 95% CIs as described in Section 5.6. These analyses will be conducted in the ITT and PP analysis sets.

The sensitivity analyses as proposed in Section 5.4.1 for the primary mean 24-hour SBP will be additionally conducted for the 8-week daytime and nighttime SBP.

5.5.2.2. Change in Mean Office SBP and DBP from Baseline to Time Points Post-Treatment.

The mean change in office blood pressures at all collected time points will be reported with 95% CIs as described in Section 5.6. These analyses will be conducted in the ITT and PP analysis sets.

The sensitivity analyses as proposed in Section 5.4.1 for the primary mean 24-hour SBP will be additionally conducted for the 8-week office SBP.

5.5.2.3. Percentage of Subjects Controlled to Target Blood Pressure Values.

The number and percent of patients controlled to target office blood pressure of <140 and >90 mmHg will be summarized by treatment group and compared via Fisher's Exact test. These analyses will be conducted in the ITT and PP analysis sets.

5.5.2.4. Use of Antihypertensive Medication(s) from Time of Procedure to 8 weeks Post-Treatment (Emergency Use Medication).

The mean change in the number of antihypertensive medications will be summarized as described in Section 5.7 along with 95% CIs for the mean change in number of medications. The addition of new antihypertensive drugs will be considered an intensification of the antihypertensive regimen. Discontinuation of one or more of the baseline antihypertensive medications without an increase in dose of remaining drugs or addition of new drugs will be considered a reduction in antihypertensive drug regimen.

Antihypertensive dose titration will be scored according to the protocol as defined in the tables below. The mean treatment score will be reported by treatment group and the groups compared via Fisher's Exact test. These analyses will be conducted in the ITT and PP analysis sets.

Step (Target SBP <140 mmHg and ≥90 mmHg)[1]	**Drug**	**Treatment Score[2]**
0 (not needed)	None	0
1 (if needed)	CCB: mid-dose	1
2 (if needed)	ACE inhibitor or ARB: full dose	2
3 (if needed)	Hydrochlorothiazide 12.5 mg	3
4 (if needed)	Hydrochlorothiazide 25 mg	4
5 (if needed)	CCB: increase to full dose	5
6 (if needed)	Spironolactone or beta-blocker or clonidine	6
7 (if needed)	Spironolactone or beta-blocker or clonidine	7
8 (if needed)	Spironolactone or beta-blocker or clonidine	8

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; SBP = systolic blood pressure.

1. There will usually be 2 to 3 weeks between steps. If the target is reached, there are no further steps even if BP fluctuates above the target. If initial systolic blood pressure (SBP) is ≥160 mmHg, Steps 1 and 2 can be combined. Fixed-combination drug products can be used to decrease pill burden.
2. The treatment score will be used for the purpose of the statistical analysis.

Source: Weber et al. 2015

5.5.2.5. Use of Antihypertensive Medication(s) (including Increases/Decreases) from 8 weeks to 6 months Post-Treatment (Titrated According to Standardized Formula to Maintain a Target SBP of <140 mmHg and ≥90 mmHg).

The mean change in the number of antihypertensive medications will be summarized as described in Section 5.7 along with 95% CIs for the mean change in number of medications. The addition of new antihypertensive drugs will be considered an intensification of the antihypertensive regimen. Discontinuation of one or more of the baseline antihypertensive medications without an increase in dose of remaining drugs or addition of new drugs will be considered a reduction in antihypertensive drug regimen.

The mean treatment score will be reported by treatment group and the groups compared via Fisher's Exact test. These analyses will be conducted in the ITT and PP analysis sets.

5.5.2.6. Compliance with Not Taking Antihypertensive Medications Through 8 weeks Post-Treatment.

The number and percent of patients in whom no antihypertensive medications are detected according to urine compliance results will be summarized by treatment group and compared using Fisher's Exact test. Subjects who meet the protocol defined criteria for antihypertensive drug treatment and receive treatment within 8 weeks will be excluded from the analysis. These analyses will be conducted in the ITT and PP analysis sets.

5.5.2.7. Use of Antihypertensive Medication(s) according to Defined Daily Dose.

In addition to the protocol specified analyses as described above, prescribed medications will be summarized according to the sum of the defined daily dose (DDD) in order to assess and

compare total drug consumption between groups (World Health Organization Collaborating Centre for Drug Statistics, 2019). The data will be expressed as DDD/100 patient days.

5.6. Blood Pressure

Blood pressure will be summarized at each visit for the various blood pressure measures: office BP (Screening (Week -8), run-in (Week -2), baseline (Week -1), 4 weeks, 8 weeks, 3 months, 6 months, 1 year and 2 years), 24-hour ABPM (baseline [Week -1], 8 weeks, 6 months and 1 year), daytime ABPM (baseline [Week -1], 8 weeks, 6 months and 1 year) and nighttime ABPM (baseline [Week -1], 8 weeks, 6 months and 1 year). Both systolic and diastolic blood pressure will be presented separately. The mean values at each visit will be presented along with the mean change from baseline (and the matched baseline data for each visit).

The number and percentage of subjects with any decrease from baseline in the various blood pressure measures will be presented. The number and percentage of subjects with any, ≥5 mmHg, ≥10 mmHg, and ≥20 mmHg decreases in blood pressure at each time point will be presented.

Ninety-five percent CIs for the change in mean blood pressure will be computed as well as the 95% CI for the percentage of subjects with any decrease in blood pressure.

These analyses will be conducted in the ITT analysis set.

In order to assess the totality of the data over time, changes in blood pressure at the 8-week, 3-month, 6-month, and 1-year and 2-year (office BP only) visits will be plotted over time by treatment group and assessed via a mixed effects repeated measures model. All available data at the time of analysis will be included in the model. This analysis will be conducted in the ITT analysis set with available data.

5.7. Antihypertensive Medications

The mean number of antihypertensive medications will be summarized at baseline, 8 weeks, 6 months, 1 year and 2 years. The number and percentage of patients on 0 to 3, and >3 medications will additionally be presented. The mean change from baseline in the number of antihypertensive medications at each visit will be presented along with the matched baseline mean values. Antihypertensive medications will also be summarized by class. These analyses will be conducted in the ITT Analysis Set.

5.8. Adverse Experiences

5.8.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) per the data management plan for the study. Summary statistics for AEs will be presented by MedDRA system organ class and preferred term.

Treatment-emergent AEs (TEAEs) are defined as AEs that meet one of the following criteria:

- Have a start date and time during or after the procedure
- Have a missing start date, and the stop date is after the procedure

- Have a start date and time before the procedure, but have a worsening severity during or after the procedure.

Overall summary statistics (number of events, and number and percentage of subjects) will be prepared by treatment group for the following treatment-emergent events: TEAEs, related TEAEs, SAEs, related SAEs, MAEs, related MAEs (per investigator and CEC adjudication), AEs leading to study discontinuation, AEs leading to procedure interruption/discontinuation, and deaths.

Related AEs are those AEs that are recorded as being related to the study procedure/treatment. Events for which the relationship is not recorded will be considered as related for the purpose of the tabular summaries.

Rates of AEs (serious and non-serious), peri-procedurally, at discharge, and at each of the follow-up time points will be summarized cumulatively as follows:

- Frequency (number and percentage of subjects) with TEAEs, overall and by MedDRA system organ class and preferred term
- Frequency (number and percentage of subjects) with treatment-emergent SAEs, overall and by MedDRA system organ class and preferred term
- Frequency (number and percentage of subjects) with each site-reported treatment-emergent AE or SAE, by relationship to the investigational device or procedure according to both the investigator and the CEC (SAEs only)
- Frequency (number and percentage of subjects) with each site-reported treatment-emergent AE or SAE, by severity.

These analyses will be conducted in the Safety Analysis Set.

AEs and SAEs that start before the procedure (i.e. which are not treatment-emergent) will also be listed for all enrolled subjects, including screen failures.

5.8.1.1. Listing of Adverse Events by Patient

A by-patient listing of all adverse events reported, including date started/stopped, seriousness, intensity, relationship to study drug, action taken, and outcome will be presented in the data listings. TEAEs will be flagged in the listing.

5.8.1.2. Listing of Device Deficiencies by Patient

A by-patient listing of any device deficiency reported will be included in the data listings.

5.9. Imaging Core Laboratory Findings

5.9.1. MRA/CT Angiogram

Results of the magnetic resonance angiography (MRA)/computed tomography (CT) assessments will be summarized at each imaging visit (baseline and 6 months) for all subjects by treatment group. These analyses will be conducted in the ITT Analysis Set.

5.9.2. Duplex Ultrasound Findings

Results of the duplex ultrasound (DUS) will be summarized at 6 months for all subjects by treatment group. These analyses will be conducted in the ITT Analysis Set.

5.10. Clinical Laboratory Evaluation

Laboratory measurements, including chemistry, hematology, coagulation panel, and urinalysis, will be summarized at each visit, as applicable, and shift tables will be presented for changes from baseline to post-baseline at 8 weeks, 6 months, 1 year and 2 years. These analyses will be conducted in the Safety Analysis Set.

5.10.1. Listing of Laboratory Values by Patient

A by-patient listing of all laboratory values will be included.

5.11. Physical Exam

Physical exam will be summarized at each visit (baseline, discharge, 4 weeks, 8 weeks, 6 months, 1 year and 2 years). These analyses will be conducted in the ITT Analysis Set.

5.12. Electrocardiogram Findings

Electrocardiogram findings will be summarized at screening and 6 months. Any new abnormality at 6 months will summarized.

5.13. Additional Concomitant Medications

5.13.1.1. Listing of Concomitant Medications by Patient

A by-patient listing of all concomitant medications reported, drug name, indication, date started/stopped, dose, and route of administration, will be presented in the data listings. This listing will include all antihypertensive medications as well as any other medications reported during the trial.

5.14. Treatment Perception

The treatment perception questionnaire will be summarized at procedure and 8 weeks. The Bang (Bang, 2004) and James (James, 1996) blinding indices will be calculated and provided along with 95% CIs. These analyses will be conducted in the ITT Analysis Set.

5.15. Nephrologist Consult

The nephrologist consult comments will be provided as a data listing.

6. CHANGES TO ANALYSES PLANNED IN THE PROTOCOL

There are no changes to the planned analyses in the protocol.

7. CHANGES TO THE STATISTICAL ANALYSIS PLAN

Version / Date	Old Analysis	New Analysis	Reason for change
2.0 28Sep2020	*n/a*	Telephone contacts at 2 and 6 weeks in Ireland only added.	*Updated per Protocol V6.0*
		Those protocol deviations associated with COVID-19 will be additionally summarized separately.	*Per FDA guidance*
		Subgroups added: • Region (US vs Europe) • Ethnicity (US only) • Race (US only)	*Updated per Protocol V6.0*
		Analysis windows clarified and description expanded	*Clarification*
		Added repeated measures analysis of blood pressure.	*Oversight*
3.0 08Dec2020	8-week primary analysis window not defined, assumed to be per the protocol	8-week primary analysis window expanded.	*Addition, clarification*
	No imputation specified for primary analysis	Imputation of data for subjects who meet the criteria for antihypertensive drug treatment for the primary analysis clarified.	*Clarification*
	n/a	Sensitivity analyses added for all 8-week BP measures	*Addition*
	n/a	Exploratory hierarchical analysis added	*Addition*
	Comparison between groups for BP measurements via t-test	Comparison between group for BP measures by ANCOVA adjusting for baseline BP	*Per FDA guidance for the Target BPI study, and for consistency between the 2 studies*
4.0 19Nov2021	n/a	Two unblinded team members (either two statisticians or a statistician and a statistical programmer) will be assigned for all analyses.	*CAPA-00012*

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9. STATISTICAL TABLES TO BE GENERATED

Disposition/Demographics

Table 14.1.1 Subject Disposition (Main Study)
Table 14.1.1 Subject Disposition (Crossover Phase)
Table 14.1.1-2 Screen Failures
Table 14.1.2-1 Baseline Demographics and Medical/Surgical History - ITT Analysis Set
Table 14.1.2-2 Baseline Demographics and Medical/Surgical History – Safety Analysis Set
Table 14.1.2-3 Baseline Demographics and Medical/Surgical History – PP Analysis Set
Table 14.1.3-1 Procedure Information - ITT Analysis Set
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Table 14.1.3-3 Procedure Information RENAL ARTERY TREATMENT - ITT Analysis Set

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Table 14.2.1-1 Primary Endpoint: 24-Hour Systolic Ambulatory Blood Pressure at 8 weeks - ITT Analysis Set
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Table 14.2.1-3 Primary Endpoint: 24-Hour Systolic Ambulatory Blood Pressure at 8 weeks, by Site - ITT Analysis Set
Table 14.2.1-4 Primary Endpoint: 24-Hour Systolic Ambulatory Blood Pressure at 8 weeks, by Age - ITT Analysis Set
Table 14.2.1-5 Primary Endpoint: 24-Hour Systolic Ambulatory Blood Pressure at 8 weeks, by Gender - ITT Analysis Set
Table 14.2.1-6 Primary Endpoint: 24-Hour Systolic Ambulatory Blood Pressure at 8 weeks, by Region (US vs Europe) – ITT Analysis Set
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Table 14.2.2-3 24-Hour Ambulatory Blood Pressure at 8 weeks, 6 months and 1 Year, by baseline daytime ambulatory SBP >140 mmHg and DBP <90 mmHg - ITT Analysis Set
Table 14.2.2-4 Exploratory analysis of 24-Hour Systolic Ambulatory Blood Pressure at 8 weeks HIERARCHICAL MODEL - ITT Analysis Set
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Table 14.2.3-1 Daytime Ambulatory Blood Pressure at 8 weeks, 6 months and 1 Year ALL AVAILABLE DATA - ITT Analysis Set
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Table 14.2.3-3 Daytime Ambulatory Blood Pressure at 8 weeks, 6 months and 1 Year, by baseline daytime ambulatory SBP >140 mmHg and DBP <90 mmHg - ITT Analysis Set
Table 14.2.3-4 Daytime Ambulatory Systolic Blood Pressure at 8 weeks SENSITIVITY ANALYSES – ITT Analysis Set
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Table 14.2.4-1 Nighttime Ambulatory Blood Pressure at 8 weeks, 6 months and 1 Year ALL AVAILABLE DATA - ITT Analysis Set
Table 14.2.4-2 Nighttime Ambulatory Blood Pressure at 8 weeks, 6 months and 1 Year ALL AVAILABLE DATA - PP Analysis Set
Table 14.2.4-3 Nighttime Ambulatory Blood Pressure at 8 weeks, 6 months and 1 Year, by baseline daytime ambulatory SBP >140 mmHg and DBP <90 mmHg - ITT Analysis Set
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Table 14.2.6-1 Antihypertensive Medication Use EMERGENCY USE MEDICATIONS - ITT Analysis Set
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Table 14.2.8-1.1 Office Systolic Blood Pressure at all time points - ITT Analysis Set
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Table 14.3.1-2.2 Treatment Emergent Adverse Events Peri-procedural, by Relationship - Safety Analysis Set
Table 14.3.1-2.3 Treatment Emergent Adverse Events through Discharge, by Relationship - Safety Analysis Set

Table 14.3.1-2.4 Treatment Emergent Adverse Events within 8 weeks, by Relationship - Safety Analysis Set
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Table 14.3.1-2.6 Treatment Emergent Adverse Events within 1 Year, by Relationship - Safety Analysis Set
Table 14.3.1-3.1 Treatment Emergent Adverse Events at any time during the study, by Severity - Safety Analysis Set
Table 14.3.1-3.2 Treatment Emergent Adverse Events Peri-procedural, by Severity - Safety Analysis Set
Table 14.3.1-3.3 Treatment Emergent Adverse Events through Discharge, by Severity - Safety Analysis Set
Table 14.3.1-3.4 Treatment Emergent Adverse Events within 8 weeks, by Severity - Safety Analysis Set
Table 14.3.1-3.5 Treatment Emergent Adverse Events within 6 months, by Severity - Safety Analysis Set
Table 14.3.1-3.6 Treatment Emergent Adverse Events within 1 Year, by Severity - Safety Analysis Set
Table 14.3.2-1.1 Treatment Emergent Serious Adverse Events at any time during the study, by Relationship - Safety Analysis Set
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Table 14.3.2-1.3 Treatment Emergent Serious Adverse Events through Discharge, by Relationship - Safety Analysis Set
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Table 14.3.2-2.6 Treatment Emergent Serious Adverse Events within 1 Year, by Severity - Safety Analysis Set
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Table 14.3.3-1.3 Treatment Emergent Non-Serious Adverse Events through Discharge, by Relationship - Safety Analysis Set
Table 14.3.3-1.4 Treatment Emergent Non-Serious Adverse Events within 8 weeks, by Relationship - Safety Analysis Set

Table 14.3.3-1.5 Treatment Emergent Non-Serious Adverse Events within 6 months, by Relationship - Safety Analysis Set
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Table 14.3.7-1 eGFR (mL/min/1.73m3) - Safety Analysis Set
Table 14.3.7-2.1 Summary of Laboratory Parameters (Serum Chemistry) - Safety Analysis Set
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Table 14.3.7-2.3 Summary of Laboratory Parameters (Hematology) - Safety Analysis Set
Table 14.3.7-2.4 Summary of Laboratory Parameters (Coagulation) - Safety Analysis Set
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Table 14.3.8 Physical Examination – ITT Analysis Set
Table 14.3.9 Electrocardiogram – ITT Analysis Set
Table 14.3.10 Procedural Angiogram Core Lab Analysis - ITT Analysis Set
Table 14.3.11-1 Renal Imaging Core Lab Analysis – ITT Analysis Set
Table 14.3.11-2 Renal Imaging Core Lab Analysis - ITT Analysis Set
Table 14.3.12 Renal Duplex Ultrasound (RDUS) at 6 Months – ITT Analysis Set
Table 14.4 Protocol Deviations - ITT Analysis Set
Table 14.5.1 Treatment Perception - ITT Analysis Set
Table 14.5.2 Treatment Perception BANG and JAMES BLINDING INDICES - ITT Analysis Set

10. DATA LISTINGS TO BE GENERATED

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Listing 16.2.1-2 Discontinued Subjects
Listing 16.2.2 Protocol Deviations
Listing 16.2.3 Patients excluded from efficacy analysis
Listing 16.2.4 Demographics and Medical/Surgical History
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Listing 16.2.7-1 All Adverse Events
Listing 16.2.7-2 Serious Adverse Events
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Listing 16.2.8 Laboratories
Listing 16.2.9-1 Anti-Hypertensive Medications
Listing 16.2.9-2 Other Concomitant Medications
Listing 16.2.10 Device Deficiency
Listing 16.2.11 ECG and MR/CT Angiogram
Listing 16.2.12 DUS
Listing 16.2.13 Nephrologist Consult

11. FIGURES TO BE GENERATED

Figure Number	Title
Figure 1.1	Mean Office SBP and DBP by Visit
Figure 1.2	Mean Change from Baseline in Office SBP and DBP by Visit
Figure 1.3	Office SBP over time by Subject
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Figure 5	Mean eGFR ($mL/min/1.73m^2$) over time
Figure 6	Kaplan Meier plot of CEC Adjudicated MAE

APPENDIX A – TABLE SHELLS