PROTOCOL SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	**Combination Product:** Peregrine System™ Kit (also referred to as Peregrine Kit) **Drug Part:** Dehydrated Alcohol Injection, USP (also referred to as alcohol, dehydrated alcohol, ethanol, absolute ethanol, ethyl alcohol, or absolute alcohol) **Device Part:** Peregrine System™ Infusion Catheter (also referred to as Peregrine Catheter)
Name(s) of Active Ingredient(s)	Dehydrated Alcohol Injection, USP
CLINICAL CONDITION(S)/INDICATION(S) Hypertension	
Protocol ID	CR0014
Protocol Version and Date	7.0 14 DEC 2021
EudraCT Number	2018-000036-96
Protocol Title	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
Short Title	The TARGET BP OFF-MED Trial
Study Phase	Phase 2 (Proof-of-Concept)
PLANNED STUDY PERIOD	
Initiation	MAY 2018
Primary Endpoint Completion	JUN 2021
Study Completion	MAR 2023
Duration	Approximately 5.0 years
STUDY OBJECTIVES AND PURPOSE	
Study Purpose To obtain an assessment of the efficacy and safety of renal denervation by alcohol-mediated neurolysis using the Peregrine Kit in hypertensive subjects in the absence of antihypertensive medications.	
Primary Objective • To evaluate the efficacy of renal denervation by alcohol-mediated neurolysis using the 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 • 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. • 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.	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Proof-of-Concept for efficacy (ambulatory blood pressure monitoring [ABPM], office blood pressure)
Control Type	Sham Treatment
Study Indication Type	Treatment
Intervention Model	Parallel
Blinding/Masking	Blinded (The subject, sponsor, and hypertensionist/nephrologist performing the screening and follow-up assessments are blinded. The interventionalist and cath lab staff are unblinded.)
Study Design	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 attend the study site for the day of procedure. All subjects will receive sedation and analgesia and undergo a diagnostic renal angiogram per standard procedures. Note: the type of sedation and analgesia will take into account the subject's preference, the interventionalist's and anesthesiologist's standard of practice, and institutional policy for this type of procedure. Subjects will then 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 is 4 x 0.6 mL = 2.4 mL.) • Sham Control Arm: only renal angiography 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. The study will be unblinded after the last subject has completed the 1-year follow-up 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 1-year data from all subjects and the study has been unblinded.
Study Geography/ Number of Planned Investigational Sites	United States (US) and Europe Multicenter trial with approximately 25 investigational sites (in the US and Europe)
Number of Groups/ Arms/Cohorts	2 groups (Treatment Arm, Sham Control Arm; randomized 1:1)
Number of Targeted Subject Treatment, Total and in Each Arm	Approximately 90 subjects randomized: • 45 subjects in the Treatment Arm • 45 subjects in the Sham Control Arm
Planned Duration of Subject Participation	Approximately 26 months* (for each subject) • Screening period: approximately 4 to 8 weeks • Run-in period: 4 weeks • In-hospital period: 2 days • Follow-up period: 2 years *May be different for subjects in Sham Control Arm in the case of crossover: subjects will have a final 1-year follow-up visit after crossover treatment.
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Combination Product:** Peregrine System Kit **Drug Constituent Part:** Dehydrated Alcohol Injection, USP **Device Constituent Part:** Peregrine System Infusion Catheter **Dose:** 0.6 mL alcohol per treated renal artery. Maximum total dose per subject = 2.4 mL at one treatment session (i.e. during the same procedure). **Dosage form:** Solution for injection **Dosage frequency:** Once during the study procedure **Mode of administration:** Direct infusion to the perivascular space, during an endovascular procedure using the device constituent part
Placebo/Control/ Comparator	In the Sham Control Arm, only renal angiography will be performed. No alcohol infusion (i.e. no renal denervation) will be performed. **Dosage form:** Not applicable **Dosage frequency:** Once during the study procedure Mode of administration: Endovascular

SUBJECT SELECTION

Subjects will be enrolled in the study at the time they sign the informed consent form. No study-specific procedures will be performed until after the subject has provided written informed consent.

Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible and undergo the procedure:

Prior to run-in period

1. Subject has provided written informed consent.
2. Male or female subject, aged ≥18 and ≤80 years at time of enrollment.
3. If subject has a documented history of uncontrolled hypertension (see definition in Definition of Terms section of protocol) and is currently taking no (0) antihypertensive medications, he/she must:
   - Have 3 office blood pressure measurements with a mean office systolic blood pressure (SBP) of ≥140 mmHg and ≤180 mmHg AND mean office diastolic blood pressure (DBP) ≥90 mmHg, and
   - Be willing to adhere to the no-medication regimen for at least 12 weeks (4-week run-in period and 8-week post-treatment period).
4. If subject has a documented history of uncontrolled hypertension (see definition in Definition of Terms section of protocol) and is currently taking 1 or 2 antihypertensive medications, he/she must:
   - Have 3 office blood pressure measurements with a mean office SBP of ≥120 mmHg and ≤180 mmHg and
   - Be willing to discontinue his/her antihypertensive medication(s), and to adhere to the no-medication regimen for at least 12 weeks (4-week run-in period and 8-week post-treatment period).
5. Investigator judges that the subject can be discontinued safely from all current antihypertensive medication (where applicable) and managed safely for at least 12 weeks (4-week run-in period and 8-week post-treatment period) without antihypertensive medication intake.
6. Female subjects of childbearing potential must agree to use acceptable methods of contraception (as defined in the protocol), from the time of informed consent through to the last follow-up visit.
7. Subject agrees to have all study procedures performed and is able and willing to comply with all study follow-up visits and protocol requirements.

End of run-in period

8. Subject has 3 office blood pressure measurements with a mean office SBP of ≥140 mmHg and ≤180 mmHg AND mean office DBP ≥90 mmHg.
9. Subject has a mean 24-hour ambulatory SBP of ≥135 mmHg and ≤170 mmHg with ≥70% valid readings (as determined by ABPM measurement device).

Exclusion Criteria

If **ANY** of the following exclusion criteria are met, the subject must be excluded from the trial and cannot be randomized or undergo the procedure:

1. Subject has a contraindication known for conventional percutaneous interventional procedures such as:
   - Intolerance for antiplatelet/anticoagulant therapy
   - Known allergy to contrast media that cannot be adequately pre-medicated
   - Bleeding/coagulation disorders (such as bleeding diathesis, thrombocytopenia, and severe anemia)
   - Occlusive peripheral vascular disease that would preclude percutaneous femoral access for the procedure.

2. Subject has an acute or sub-acute infection that the investigator judges would pose unacceptable procedural risks to the subject.
3. Subject has imaging-assessed renal artery anatomy abnormalities or variations based on investigator's evaluation of the screening images (i.e. magnetic resonance angiography [MRA]/computed tomography angiography [CTA] examination and/or renal angiography) meeting one of the following criteria:
   - Main renal artery that has a diameter of <4 mm or >7 mm and length of <5 mm
   - Accessory renal arteries with diameter >2 mm or <4 mm, which supply >20% of the whole kidney parenchyma on that side, per the investigator's judgment. NOTE: subjects with more than one eligible accessory renal artery per side will be excluded.
   - Renal artery stenosis >50% of the normal diameter segment (diameter stenosis, compared to the angiographically normal proximal or distal segment)
   - Any renal artery abnormality or disease that, per the physician assessment, precludes the safe insertion of the guiding catheter (including, but not limited to, severe renal artery aneurysm, excessive tortuosity, severe renal artery calcification)
   - Previous renal angioplasty associated with stenting or other implants, that, per the physician's assessment, precludes the safe deployment of the Peregrine Catheter components in the target treatment segment of the renal artery
   - Previous renal denervation
   - Fibromuscular dysplasia of the renal arteries.
4. Subject has documented severe untreated obstructive sleep apnea (apnea hypopnea index [AHI] ≥30 per hour).
5. Subject has documented diagnosis of the following causes of hypertension: Cushing's disease or Cushing's Syndrome, hyperaldosteronism, pheochromocytoma, thyroid and parathyroid abnormalities, or onset of hypertension prior to the age of 18.
6. Subject has a history of pre-eclampsia.
7. Subject has orthostatic hypotension at screening, or documented history of orthostatic hypotension within 12 months prior to the planned procedure, defined as a drop in blood pressure that is >20 mmHg in SBP and/or >10 mmHg in DBP within 3 minutes upon standing from sitting or from a lying down face-up (supine) position.
8. Subject has Type 1 diabetes mellitus, or uncontrolled Type 2 diabetes mellitus (defined as hemoglobin A1c [HbA1c] ≥9.0%).
9. Subject has an eGFR of ≤45 mL/min/1.73 m^2, based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; or is on chronic renal replacement therapy.
10. Subject has nephrotic syndrome.
11. Subject has a history of recurrent (>1 episode) kidney stones, or history of kidney stones within 12 months prior to the planned procedure.
12. Subject has a history of nephrectomy, a single kidney or kidney tumor, or urinary tract obstruction (with potential for hydronephrosis). NOTE: Simple renal cysts are not an exclusion.
13. Subject has a renal transplant, or is known to have a non-functioning kidney or unequal renal size (>2 cm difference in renal length between kidneys associated with a chronic kidney disease or a deterioration of the kidney function).
14. Subject has a history of myocardial infarction, unstable angina pectoris, or stroke/transient ischemic attack (TIA) within 6 months prior to the planned procedure.
15. Subject has any of the following conditions: severe cardiac valve stenosis, heart failure (New York Heart Association [NYHA] Class III or IV), chronic atrial fibrillation, and known primary pulmonary hypertension (>60 mmHg pulmonary artery or right ventricular systolic pressure).

16. Subject is allergic or intolerant to the neurolytic agent (i.e. dehydrated alcohol).
17. Subject is being treated chronically (e.g. daily use) with non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressive medications, or immunosuppressive doses of steroids. Aspirin therapy and nasal pulmonary inhalants are allowed.
18. Any contraindication to the imaging as required per the protocol.
19. Subject for whom an ABPM device cannot be used due to arm size (>42 cm arm circumference) or other reasons as identified by the investigator.
20. Subject has any other acute or chronic condition that the investigator believes will adversely affect the ability to interpret the data or will prevent the subject from completing the trial procedures, or has a life expectancy of <12 months.
21. Subject has a known history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions, or for any reason, in the opinion of the investigator, would be unlikely or unable to comply with study protocol requirements.
22. If female, subject is pregnant or lactating at the time of enrollment or planning to become pregnant during the trial time period.
23. Subject has participated in another clinical study involving an investigational drug or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an investigational drug or investigational device during the course of this study. Subjects enrolled in observational registries not involving renal denervation may still be eligible.
24. Subject is in custody or an institution.
25. Subject has close affiliation with the study site or sponsor (e.g. employee, close relative of an employee).
26. Subject has a history of hypertensive emergency in the previous 3 months (see definition of hypertensive emergencies in Definition of Terms section of protocol).

ENDPOINTS AND STATISTICAL ANALYSIS

Sample Size Calculation

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.

This study is designed as a proof-of-concept study. It is 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 primary efficacy endpoint analysis).

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[1]. 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.

Endpoints and Planned Statistical Analysis

The following populations are defined for analysis:

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.

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.

Secondary efficacy endpoints:

- Change in mean 24-hour, daytime, (07:00 to 21:59), and nighttime (22:00 to 06:59) ambulatory SBP and DBP from baseline to time points post-treatment.
- Change in mean office SBP and DBP from baseline to time points post-treatment.
- 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 and 1-year post-treatment (titrated according to standardized formula to maintain a target SBP of <140 mmHg and ≥90 mmHg).
- Compliance with not taking antihypertensive medications through 8 weeks post-treatment.

Changes from baseline will be computed as the paired mean difference and will be summarized with descriptive statistics (n, mean, SD, range, median). The 95% confidence interval (CI) of the difference between treatment groups at each time point will be computed. Categorical data will be summarized as frequencies and percentages. Relative risks and 95% CIs will be computed. Secondary efficacy endpoints are considered supportive and thus there is no adjustment to alpha for multiplicity with a single primary efficacy endpoint. Analysis of efficacy endpoints will be conducted in the ITT and PP Analysis Sets. For the primary efficacy endpoint analysis, the main population is considered the ITT, and the PP is considered supportive.

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.

It is planned to conduct an 8-week blinded interim analysis, a 6-month blinded interim analysis, and an unblinded 1-year interim analysis after all subjects have completed the 1-year follow-up visit and the study has been unblinded.

Secondary safety endpoints:

- Major adverse events (MAEs) through 30 days post-treatment, as adjudicated by the Clinical Events Committee (CEC). An MAE is defined as any of the following:

[1] Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet 2017;390(10108):2160-70.

- 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, 6 months, and 1-year post-treatment.
- Decreases in eGFR >25% from baseline to 8 weeks, 6 months, and 1-year post-treatment.
- Rate of adverse events (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).

The percentage of subjects with any MAE through 30 days post-treatment will be displayed by treatment group. The relative risk will be displayed with 95% CIs. The 2 groups will be compared using Fisher's exact test.

Other safety endpoints will be summarized as frequencies and percentages. Relative risks and 95% CIs will be computed. Analysis of all safety endpoints will be conducted using the Safety Analysis Set.

Table 1 Schedule of Study Assessments (Main Study)

Period	**Scrn Period**	**Run-In Period[1]**			**In-Hospital Period**		**Follow-Up Period**						**ET[2]**
Visit Time Point	**Up to Wk -8**	**Wk -4**	**Wk -2**	**Wk -1 (Baseline)**	**D 0[3]**	**D 1**	**D 2 to D 4 (48-96 h)[4]**	**Wk 4**	**Wk 8**	**Mth 3**	**Mth 6**	**Yr 1 and 2**	
Visit Window			**+/-4 D**	**+/-2 D**				**+/-7 D**	**+/-7 D**	**+/-2 Wk**	**+/-4 Wk**	**+/-8 Wk**	
Informed consent	X												
Eligibility check	X			X									
Demographic data	X												
Medical history	X												
Office BP pressure[5]	X		X	X				X	X	X	X	X	X
24-hour ABPM[6]				X[7]					X		X	X[8]	
MRA/CTA[9]	X[10]										X[11]		
Post-contrast serum creatinine[12]	X[4]						X[4]				X[4]		
Blood sample[13]	X[14]			X	X*[15]			X[16]	X		X	X	X
Urine sample[13]				X				X[16]	X		X	X	X
Pregnancy test (serum)	X			X					X		X	X	X
No antihypertensive meds permitted[17]		X→	→	→	→	→	→	→	→X				
Antihypertensive meds, if required[18]									X→	→	→	→	
Physical examination, vital signs[19]	X		X	X	X*	X		X	X	X	X	X	X
12-lead ECG	X										X		

Period	**Scrn Period**	**Run-In Period[1]**			**In-Hospital Period**		**Follow-Up Period**						**ET[2]**
Visit Time Point	**Up to Wk -8**	**Wk -4**	**Wk -2**	**Wk -1 (Baseline)**	**D 0[3]**	**D 1**	**D 2 to D 4 (48-96 h)[4]**	**Wk 4**	**Wk 8**	**Mth 3**	**Mth 6**	**Yr 1 and 2**	
Visit Window			**+/-4 D**	**+/-2 D**				**+/-7 D**	**+/-7 D**	**+/-2 Wk**	**+/-4 Wk**	**+/-8 Wk**	
Nephrologist/ hypertension specialist review	X												
Renal duplex ultrasound											X[11]		
Dispense/review subject diary		X	X	X	X	X		X	X				
Subject completes diary[20]		X→	→	→	→	→	→	→	→X				
Renal angiography					X*						X[11]		
Randomization					X*[21]								
Renal denervation (if randomized to this arm)					X*								
Treatment perception assignment questionnaire					X[22]				X				
Product performance and procedural safety					X*								
Product accountability					X*								
AE collection[23]	X→	→	→	→	→*	→	→	→	→	→	→	→X	X
Prior/concomitant medications[24]	X→	→	→	→	→*	→	→	→	→	→	→	→X	X

Period	Scrn Period	Run-In Period[1]			In-Hospital Period		Follow-Up Period						ET[2]
Visit Time Point	**Up to Wk -8**	**Wk -4**	**Wk -2**	**Wk -1 (Baseline)**	**D 0[3]**	**D 1**	**D 2 to D 4 (48-96 h)[4]**	**Wk 4**	**Wk 8**	**Mth 3**	**Mth 6**	**Yr 1 and 2**	
Visit Window			**+/-4 D**	**+/-2 D**				**+/-7 D**	**+/-7 D**	**+/-2 Wk**	**+/-4 Wk**	**+/-8 Wk**	
Discharge from study site						X							
Possible crossover from Sham Control Arm[25]												X	

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; BP = blood pressure; CTA = computed tomography angiography; D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; HR = heart rate; MAE = major adverse event; MRA = magnetic resonance angiography; Mth = month; SAE = serious adverse event; Scrn = screening; Wk = week; Yr = year

*Peri-procedural AE and concomitant medication recording, as well as all assessments performed in the cath lab/special procedure lab and/or in relation to the procedure, will be performed by unblinded personnel.

1 The run-in period starts approximately 4 weeks prior to the planned date of the procedure. The subject must start the run-in period on 0 antihypertensive medications. In the case of subjects taking 1 or 2 antihypertensive medications that require down-titration, these subjects must down-titrate their medications prior to the start of the run-in period. If a subject takes antihypertensive medication during the run-in period but still wishes to enter the study, one re-start of the run-in period is possible if this is acceptable to the physician as well as the subject, and if the physician believes that the subject will be compliant.

2 Where possible, subjects who discontinue early from the study will undergo these procedures.

3 Subjects may be admitted on Day -1 for logistical reasons. 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.

4 For applicable subjects only (see footnote 12).

5 One set of 3 measurements using the same cuff and same arm as used at screening. See office blood pressure manual.

6 ABPM measurements must be collected at the same time as office BP measurements, where applicable. Office BP measurements are collected before ABPM set-up.

7 24-Hour ABPM at this time point is only performed if office BP measurements meet the inclusion criteria.

8 At 1 year only.

9 An MRA will be performed for assessment of renal vasculature. For sites that would prefer to use CTA instead, agreement may be reached with the sponsor on a case-by-case basis (depending upon local regulatory approvals and site capacity).

10 Scheduled at the initial screening visit, then performed and assessed prior to the start of the run-in period to check renal artery anatomy. If either of the imaging tests has been performed within 12 months prior to the time of enrolment, review of the images by the core lab may be performed, with consultation by the sponsor and principal investigator, to determine if a repeat of the protocol imaging test is needed to assess anatomical eligibility. Must be performed after screening serum creatinine sampling and only to be performed if eGFR based on this sample is >45 mL/min/1.73 m^2.

11 If the renal duplex ultrasound assessment at 6 months cannot be performed, or if the results are non-diagnostic, CTA/MRA/renal angiography may be performed if agreed with the sponsor (depending upon local regulatory approvals and site capacity). If renal artery stenosis of >60% or any other significant abnormality is suspected or confirmed by renal duplex ultrasound, as evaluated by the core laboratory, or as the result of other clinical assessments, those findings should be confirmed using the imaging modality used at screening (CTA/MRA/renal angiography). The choice of imaging may be changed at the discretion of the investigator and should be discussed with the sponsor.

12 Subjects with an eGFR of ≥45 and <60 mL/min/1.73 m^2 based on the screening serum creatinine sample will undergo blood sampling for post-contrast serum creatinine measurement 48-96 hours after imaging at screening. Subjects with an eGFR of ≥45 and <60 mL/min/1.73 m^2 based on the Week -1 (baseline) serum creatinine sample will undergo blood sampling for post-contrast serum creatinine measurement 48-96 hours after imaging during the procedure and any subsequent procedure where imaging contrast is used.

13 See Table 3 for details of blood and urine parameters. Tests to be done in the case of ET will be as for the Month 6 visit, but excluding compliance tests.

14 For measurement of serum creatinine only (all subjects). This sample must be taken prior to imaging at screening, because the eGFR value based on this measurement will be used to assess whether the subject is excluded or may proceed to have the screening imaging assessment.

15 Activated coagulation time (ACT) only is performed on Day 0, per the hospital's standard of care.

16 For compliance testing only.

17 No antihypertensive medications are permitted from the start of the run-in period until the subject has completed the visit at 8 weeks post-treatment (except in the case of emergencies).

18 Antihypertensive medications may be given after the 8-week visit if necessary (according to pre-defined criteria and proposed titration schedule).

19 Screening visit: full physical examination, height, weight, temperature, and HR. Week -2: abbreviated physical examination, weight, temperature, and HR; Week -1: temperature and HR; Day 0: single measurement of cuff BP and HR before and after study procedure (while in cath lab/special procedure lab); Day 1: abbreviated physical examination, single measurement of cuff BP, HR, and temperature; Weeks 4 and 8, and Month 3: weight, HR, and temperature; Month 6: full physical examination, weight, HR, and temperature; Years 1 and 2: weight, HR, and temperature; ET visit: abbreviated physical examination, weight, temperature, and HR.

20 Subjects will record BP twice daily, any antihypertensive medication(s) taken, and other notes (e.g. symptoms, illnesses). Subjects do not have to complete the subject diary during the in-hospital period.

21 Randomization will be performed in the cath lab/special procedure lab after the subject has been sedated and after renal angiography.

22 Questionnaire to be conducted post-treatment (>4 hours and <24 hours).

23 All AEs must be recorded from the time of signing the informed consent form through the end of study participation.

24 All medications (prescribed or over-the-counter, including supplements) must be recorded from the time of signing the informed consent form through the 6-month follow-up visit (or time of early termination from the study, if prior to 6 months). All antihypertensive medications must be recorded starting from the time of signing the informed consent form through the 2-year follow-up visit (or time of early termination from the study). In addition, all medications (prescribed or over-the-counter, including supplements) taken within 14 days prior to the onset of a serious AE (SAE) or major AE (MAE), as well as during the SAE or MAE timeframe, must be recorded starting from the time of signing the informed consent form through the 2-year follow-up visit (or time of early termination from the study).

25 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 1-year data from all subjects and the study has been unblinded.

Table 2 Schedule of Study Assessments (Crossover Phase)

Period	**Re-Screening Period**	**In-Hospital Period**		**Follow-Up Period**			**ET[1]**
Visit Time Point	**Up to Wk -4**	**D 0[2]**	**D 1**	**D 2 to D 4 (48-96 h)[3]**	**Wk 4**	**Mth 6**	
Visit Window					**+/-7 D**	**+/-4 Wk**	
Informed consent	X						
Eligibility check[4]	X						
Office BP pressure[5]	X				X	X	X
MRA/CTA	X[6]					X[7]	
Renal angiography		X				X[7]	
Post-contrast serum creatinine[8]	X[3]			X[3]		X[3]	
Blood sample[9]	X	X[10]			X	X	X
Urine sample[9]	X				X	X	X
Pregnancy test (serum)	X				X	X	X
Physical examination, vital signs[11]	X	X	X		X	X	X
12-lead ECG						X	
Renal duplex ultrasound						X[7]	
Renal denervation		X					
Product performance and procedural safety		X					
Product accountability		X					
AE collection[12]	→	→	→	→	→	→	X
Prior/concomitant medications[13]	→	→	→	→	→	→	X
Discharge from study site			X				

Abbreviations: AE = adverse event; BP = blood pressure; CTA = computed tomography angiography; D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; HR = heart rate; MAE = major adverse event; MRA = magnetic resonance angiography; Mth = month; SAE = serious adverse event; Scrn = screening; Wk = week; Yr = year

1 Where possible, subjects who discontinue early from the crossover phase will undergo these procedures.

2 Subjects may be admitted on Day -1 for logistical reasons.

3 For applicable subjects only (see footnote 8).

4 Eligibility criteria for the crossover phase.

5 One set of 3 measurements using the same cuff and same arm as used at screening. See office blood pressure manual.

6 At the discretion of the investigator, an MRA will be performed again for assessment of renal vasculature to assess eligibility. For sites that would prefer to use CTA instead, agreement may be reached with the sponsor on a case-by-case basis (depending upon local regulatory approvals and site capacity).

7 If the renal duplex ultrasound assessment at 6 months cannot be performed, or if the results are non-diagnostic, CTA/MRA/renal angiography may be performed if agreed with the sponsor (depending upon local regulatory approvals and site capacity). If renal artery stenosis of >60% or any other significant abnormality is suspected or confirmed by renal duplex ultrasound, as evaluated by the core laboratory, or as the result of other clinical assessments, those findings should be confirmed using the imaging modality used at screening (CTA/MRA/renal angiography). The choice of imaging may be changed at the discretion of the investigator and should be discussed with the sponsor.

8 Blood sampling for post-contrast serum creatinine measurement is dependent on when imaging procedure is performed and the subject's eGFR measurement: blood is to be drawn and measured 48-96 hours after any procedure where imaging contrast is used and **ONLY** on subjects with an eGFR of >45 and <60 mL/min/1.73 m^2 (as measured at the study re-screening visit).

9 See Table 4 for details of blood and urine parameters. Tests to be done in the case of ET will be as for the Month 6 visit.

10 Activated coagulation time (ACT) is performed on Day 0, per the hospital's standard of care.

11 Re-screening visit: full physical examination, height, weight, temperature, and HR; Day 0: single measurement of cuff BP and HR before and after study procedure (while in cath lab/special procedure lab); Day 1: abbreviated physical examination, single measurement of cuff BP, HR, and temperature; Week 4: weight, HR, and temperature; Month 6: full physical examination, weight, HR, and temperature. ET visit: abbreviated physical examination, weight, temperature, and HR.

12 All AEs must be recorded from the time of signing the informed consent form (in the main study) through the end of the study (including crossover phase).

13 All antihypertensive medications must be recorded starting from the time of signing the informed consent form (in the main study) through the end of the study (including crossover phase) (or time of early termination, if applicable). In addition, all medications (prescribed or over-the-counter, including supplements) taken within 14 days prior to the onset of a serious AE (SAE) or major AE (MAE), as well as during the SAE or MAE timeframe, must be recorded starting from the time of signing the informed consent form (in the main study) through the end of the study (including crossover phase) (or time of early termination, if applicable).

Table 3 Schedule of Blood and Urine Sample Collection (Main Study)

Period		Scrn Period	Run-In Period			Treat-ment	Follow-Up Period					
Visit Time Point		**Up to Wk -8**	**Wk -4**	**Wk -2**	**Wk -1 (Base)**	**D 0**	**D 2 to D 4 (48-96 h)[1]**	**Wk 4**	**Wk 8**	**Mth 3**	**Mth 6**	**Yr 1 and 2**
Visit Window				**+/-4 D**	**+/-2 D**			**+/-7 D**	**+/-7 D**	**+/-2 Wk**	**+/-4 Wk**	**+/-8 Wk**
Serum chemistry	Sodium				X				X		X	X
	Potassium				X				X		X	X
	Serum chloride				X				X		X	X
	BUN/urea				X				X		X	X
	Uric acid				X				X		X	X
	Cystatin C				X				X		X	X
	Glucose				X				X		X	X
	Serum creatinine	X[2]			X		X[3]		X		X	X
	eGFR[4]	X			X		X[5]		X		X	X
Liver panel	AST (SGOT)				X				X		X	
	ALT (SGPT)				X				X		X	
	Alk phos				X				X		X	
	Bilirubin (conj)				X				X		X	
	Bilirubin (total)				X				X		X	
	LDH				X				X		X	
	Albumin				X				X		X	
	Total protein				X				X		X	
Hematology	RBC				X				X		X	
	WBC (total and differential)				X				X		X	
	HGB				X				X		X	
	HCT				X				X		X	
	Platelets				X				X		X	
Coagulation	aPTT				X							
	PT				X							
	INR				X							
	ACT[6]					X						

Period		Scrn Period	Run-In Period			Treat-ment	Follow-Up Period					
Visit Time Point		**Up to Wk -8**	**Wk -4**	**Wk -2**	**Wk -1 (Base)**	**D 0**	**D 2 to D 4 (48-96 h)[1]**	**Wk 4**	**Wk 8**	**Mth 3**	**Mth 6**	**Yr 1 and 2**
Visit Window				**+/-4 D**	**+/-2 D**			**+/-7 D**	**+/-7 D**	**+/-2 Wk**	**+/-4 Wk**	**+/-8 Wk**
Urinalysis	Specific gravity				X				X		X	X
	pH				X				X		X	X
	Glucose				X				X		X	X
	Ketones				X				X		X	X
	Protein (total)				X				X		X	X
	Bilirubin				X				X		X	X
	Hemoglobin				X				X		X	X
	Nitrite				X				X		X	X
	WBC				X				X		X	X
	RBC				X				X		X	X
	Bacteria				X				X		X	X
	Crystals				X				X		X	X
	Casts				X				X		X	X
	Spot microalbumin				X				X		X	X
	Spot creatinine				X				X		X	X
Compliance[7]	Urine test				X			X	X		X	
	Blood test				X			X	X		X	
Other	Pregnancy test (serum)	X			X				X		X	X
	HbA1c				X				X		X	X
	Renin				X				X		X	
	Aldosterone				X				X		X	
	TSH				X							

Abbreviations: ACT = activated clotting time; Alk phos = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase (serum glutamate pyruvate transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); Base = baseline; BUN = blood urea nitrogen; D = day; eGFR = estimated glomerular filtration rate; h = hour; HbA1c = hemoglobin A1c; HCT = hematocrit: HGB = hemoglobin; INR = international normalized ratio; LDH = lactate dehydrogenase; Mth = month; PT = prothrombin time; RBC = red blood cell(s); Scrn = screening; TSH = thyroid-stimulating hormone; WBC = white blood cell(s); Wk = week; Yr = year

Note: Tests to be done in the case of ET will be as for the Month 6 visit, but excluding compliance tests.

1 For applicable subjects only (see footnote 3).

2 Subjects with an eGFR of ≥45 and <60 mL/min/1.73 m^2 based on the screening serum creatinine sample will also undergo blood sampling for post-contrast serum creatinine measurement 48-96 hours after imaging at screening.

3 Subjects with an eGFR of ≥45 and <60 mL/min/1.73 m^2 based on the Week -1 (baseline) serum creatinine sample will undergo blood sampling for post-contrast serum creatinine measurement 48-96 hours after imaging during the procedure and any subsequent procedure where imaging contrast is used.

4 eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. For all subjects, if the calculated eGFR is reduced >25% from baseline (Week -1), the investigator should repeat the serum creatinine test as soon as possible, but no later than 1 week after the first test. If the repeated calculated eGFR remains >25% from baseline, the investigator should refer the subject for further renal functions evaluations, including review by a nephrologist. Similarly, if a subject's eGFR drops to ≤45 mL/min/1.73 m^2, then he/she will have renal function monitored and managed by a nephrologist as an additional safety measure following this event and until the event is resolved. In either case, the decrease in eGFR will be reported as an AE.

5 Only calculated for those subjects who have serum creatinine measured at this time point.

6 Performed per the hospital's standard of care and analyzed at site.

7 Compliance testing in relation to antihypertensive medications.

Table 4 Schedule of Blood and Urine Sample Collection (Crossover Phase)

Period		**Re-Screening Period**	**Treatment**	**Follow-Up Period**		
Visit Time Point		**Up to Wk -4**	**D 0**	**D 2 to D 4 (48-96 h)[1]**	**Wk 4**	**Mth 6**
Visit Window					**+/-7 D**	**+/-4 Wk**
Serum chemistry	Sodium	X			X	X
	Potassium	X			X	X
	Serum chloride	X			X	X
	BUN/urea	X			X	X
	Uric acid	X			X	X
	Cystatin C	X			X	X
	Glucose	X			X	X
	Serum creatinine	X		X[2]	X	X
	eGFR[3]	X		X[4]	X	X
Liver panel	AST (SGOT)	X			X	X
	ALT (SGPT)	X			X	X
	Alk phos	X			X	X
	Bilirubin (conj)	X			X	X
	Bilirubin (total)	X			X	X
	LDH	X			X	X
	Albumin	X			X	X
	Total protein	X			X	X
Hematology	RBC	X			X	X
	WBC (total and differential)	X			X	X
	HGB	X			X	X
	HCT	X			X	X
	Platelets	X			X	X

Period		Re-Screening Period	Treatment	Follow-Up Period		
Visit Time Point		**Up to Wk -4**	**D 0**	**D 2 to D 4 (48-96 h)[1]**	**Wk 4**	**Mth 6**
Visit Window					**+/-7 D**	**+/-4 Wk**
Coagulation	aPTT	X				
	PT	X				
	INR	X				
	ACT[5]		X			
Urinalysis	Specific gravity	X			X	X
	pH	X			X	X
	Glucose	X			X	X
	Ketones	X			X	X
	Protein (total)	X			X	X
	Bilirubin	X			X	X
	Hemoglobin	X			X	X
	Nitrite	X			X	X
	WBC	X			X	X
	RBC	X			X	X
	Bacteria	X			X	X
	Crystals	X			X	X
	Casts	X			X	X
	Spot microalbumin	X			X	X
	Spot creatinine	X			X	X
Other	Pregnancy test (serum)	X			X	X

Abbreviations: ACT = activated clotting time; Alk phos = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase (serum glutamate pyruvate transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BUN = blood urea nitrogen; D = day; eGFR = estimated glomerular filtration rate; h = hour; HCT = hematocrit: HGB = hemoglobin; INR = international normalized ratio; LDH = lactate dehydrogenase; Mth = month; PT = prothrombin time; RBC = red blood cell(s); Scrn = screening; WBC = white blood cell(s); Wk = week; Yr = year

1 For applicable subjects only (see footnote 2).

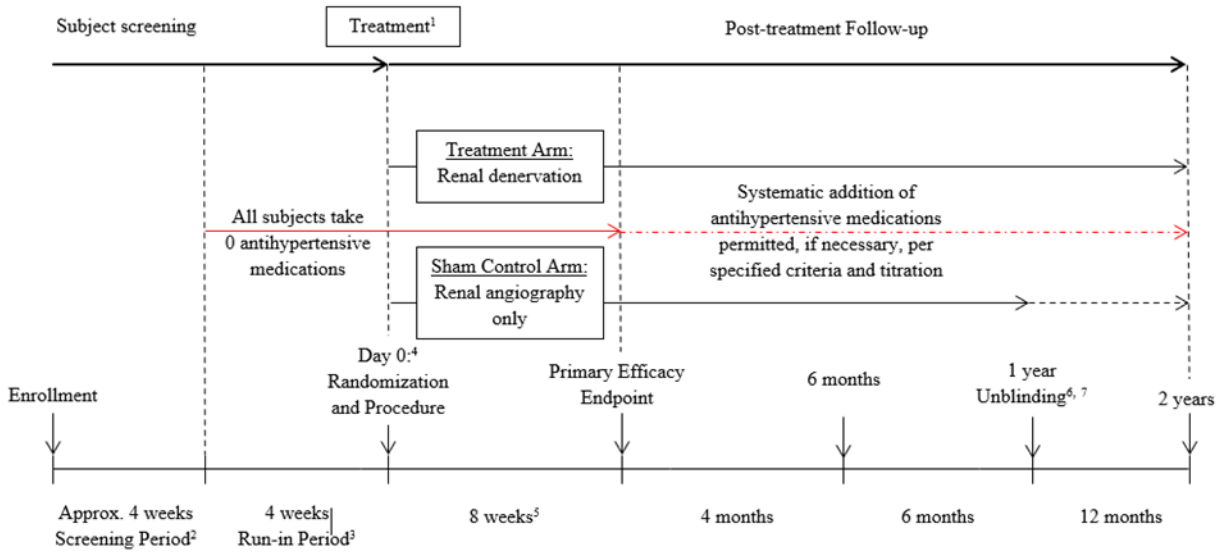
2 Blood sampling for post-contrast serum creatinine measurement is dependent on when imaging procedure is performed and the subject's eGFR measurement: blood is to be drawn and measured 48-96 hours after any procedure where imaging contrast is used and **ONLY** on subjects with an eGFR of >45 and ≤60 mL/min/1.73 m^2 (as measured at the study re-screening visit).

3 eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. For all subjects, if the calculated eGFR is reduced >25% from baseline (as measured at re-screening visit), the investigator should repeat the serum creatinine test as soon as possible, but no later than 1 week after the first test. If the repeated calculated eGFR remains >25% from baseline, the investigator should refer the subject for further renal functions evaluations, including review by a nephrologist. Similarly, if a subject's eGFR drops to ≤45 mL/min/1.73 m^2, then he/she will have renal function monitored and managed by a nephrologist as an additional safety measure following this event and until the event is resolved. In either case, the decrease in eGFR will be reported as an AE.

4 Only calculated for those subjects who have serum creatinine measured at this time point.

5 Performed per the hospital's standard of care and analyzed at site.

Figure 1 Overall Study Design



The subject, sponsor, hypertensionist/nephrologist, and research team performing the screening and follow-up assessments will be blinded to the subject's randomized treatment assignment (Treatment Arm or Sham Control Arm). The interventionalist and catheterization laboratory (cath lab) staff will be unblinded.

2 At a screening visit, after written informed consent has been provided, initial screening assessments will be made. Subjects will then attend for magnetic resonance angiography (MRA) to assess renal vasculature before the start of the run-in period. For sites that would prefer to use computed tomography angiography (CTA) instead, agreement may be reached with the sponsor on a case-by-case basis (depending upon local regulatory approvals and site capacity). Subjects must have an estimated glomerular filtration rate (eGFR) of >45 mL/min/1.73 m^2 confirmed before imaging at screening. Subjects who are currently taking antihypertensive medications will down-titrate their medications, if necessary, so that they are taking 0 antihypertensive medications at the start of the run-in period.

3 Subjects will take 0 antihypertensive medications from the start of the run-in period (Week -4). During the run-in period, a safety visit will take place approximately 2 weeks before the procedure (Week -2). Further study assessments and a final check of eligibility criteria will be performed approximately 1 week before the procedure (Week -1), including office blood pressure and ambulatory blood pressure monitoring (ABPM) measurements.

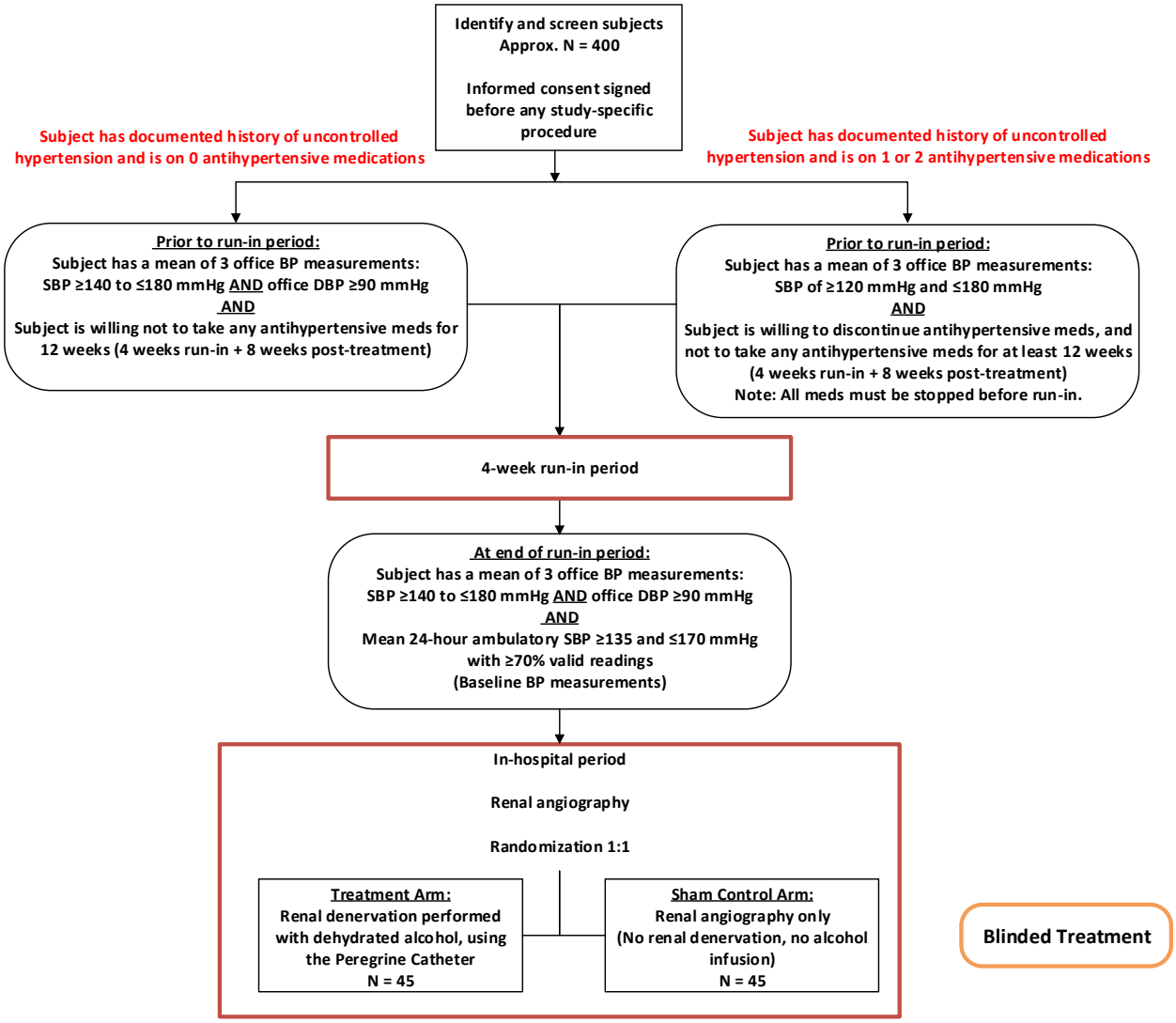
4 Subjects may be admitted on Day -1 for logistical reasons. For the day of the procedure (Day 0), flexibility in scheduling is permitted (up to 1 week), e.g. due to cath lab availability, based on physician discretion and with careful consideration of subject safety. Randomization 1:1 (Treatment Arm : Sham Control Arm) will be performed in the cath lab/special procedure lab on the day of the procedure (Day 0), after the subject has been sedated and undergone diagnostic renal angiography.

5 Subjects will continue to use 0 antihypertensive medications during the first 8 weeks after the procedure (except for emergencies). After 8 weeks, antihypertensive medications are permitted, if necessary (see Appendix I)).

6 Study unblinding will be performed after the last subject has completed the 1-year follow-up visit.

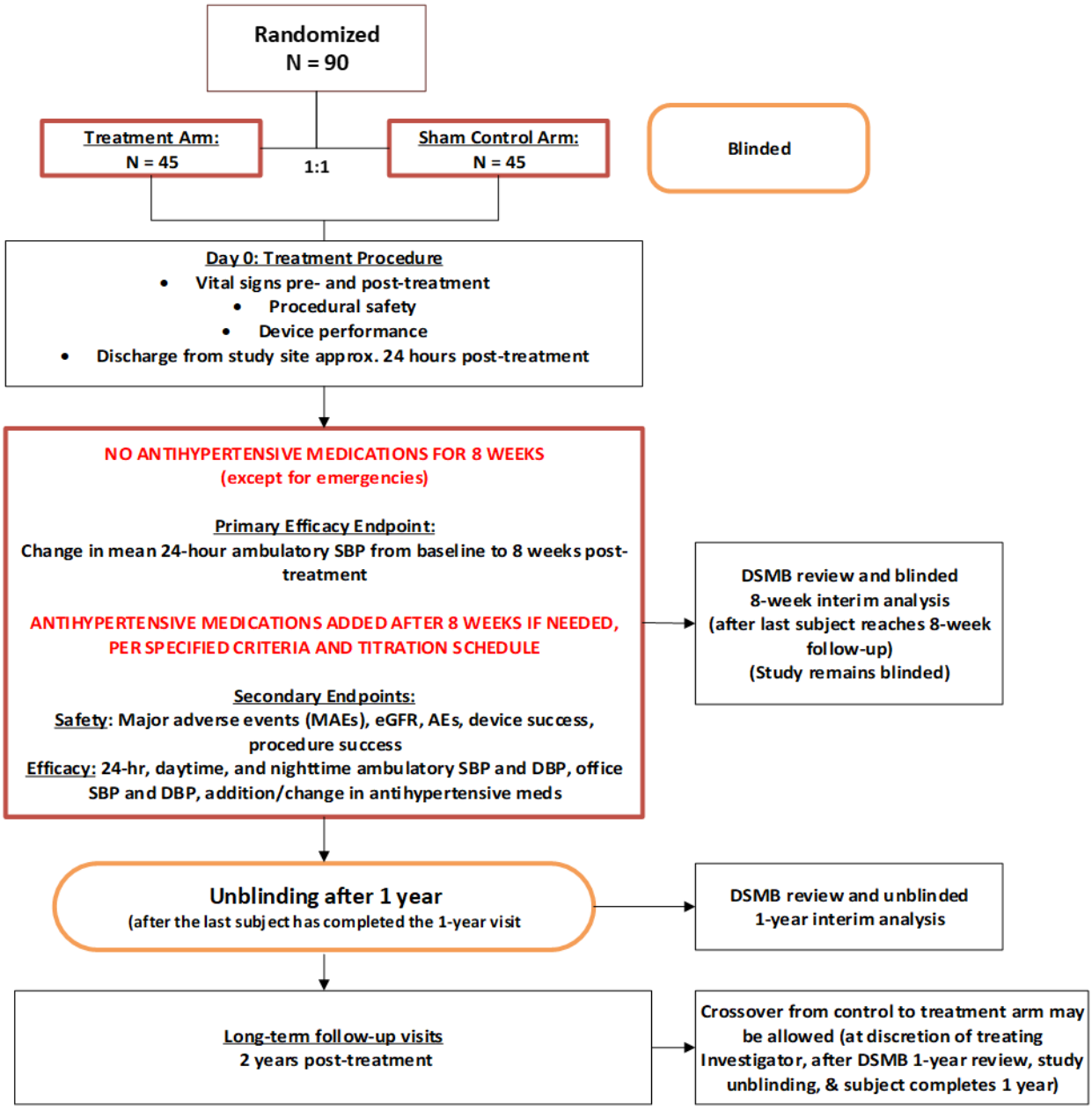
7 Crossover from the Sham Control Arm to the Treatment Arm may be allowed, at the discretion of the treating investigator, after the Data Safety Monitoring Board (DSMB) has reviewed the 1-year data from all subjects and the study has been unblinded.

Figure 2 Study Flow Diagram: Subject Screening, Run-in, and Treatment



BP = blood pressure; DBP = diastolic blood pressure; N = number of subjects; SBP = systolic blood pressure

Figure 3 Study Flow Diagram: Post-Treatment Milestones and Endpoints



AE = adverse event; BP = blood pressure; DBP = diastolic blood pressure; DSMB = Data Safety Monitoring Board; eGFR = estimated glomerular filtration rate; N = number of subjects; SBP = systolic blood pressure.

Appendix I Proposed Structured Drug Titration

After 8 weeks post-treatment, subjects may take antihypertensive medications to maintain a target office SBP of <140 mmHg and ≥90 mmHg (based on a mean of 3 measurements). The titration regimen provided in the following table should be followed if possible.

Step (Target SBP <140 mmHg and ≥90 mmHg)[1]	**Drug**	**Treatment Score**
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. For Steps 6, 7, and 8, the choice of drug and dose is at the investigator's discretion. If initial systolic BP is ≥160 mmHg, Steps 1 and 2 can be combined. Fixed-combination drug products can be used to decrease pill burden.

Source: Weber MA, Kirtane A, Mauri L, et al. Renal denervation for the treatment of hypertension: making a new start, getting it right. J Clin Hypertens 2015;17(10):743-50.