Catheter-based alcohol-mediated renal denervation for the treatment of uncontrolled hypertension: design of two sham-controlled, randomized, blinded trials in the absence (TARGET BP OFF-MED) and presence (TARGET BP I) of antihypertensive medications

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Background Arterial hypertension is a common and life-threatening condition and poses a large global health burden. Device-based treatments have been developed as adjunctive or alternative therapy, to be used with or without antihypertensive medication for treating uncontrolled hypertension. The safety and feasibility of chemical renal denervation (RDN) using the Peregrine Catheter and alcohol were demonstrated in a first-in-man and open-label clinical trials, prompting the initiation of the ongoing TARGET BP OFF-MED and TARGET BP I trials.

Design The TARGET BP trials are randomized, blinded, sham-controlled trials designed to assess the safety and efficacy of alcohol-mediated RDN for the treatment of uncontrolled hypertension in the absence of antihypertensive medications (TARGET BP OFF-MED) or in addition to prescribed antihypertensive medications (TARGET BP I). Subjects with confirmed uncontrolled hypertension and suitable renal artery anatomy are randomized (1:1) to receive either RDN using the Peregrine Kit with alcohol (0.6 mL per renal artery) infused through the Peregrine Catheter or diagnostic renal angiography only (sham procedure). TARGET BP OFF-MED completed enrollment and randomized 96 subjects. TARGET BP I will randomize approximately 300 subjects and will transition to an open-label safety cohort of approximately 300 subjects receiving RDN once the primary efficacy endpoint of the Randomized Controlled Trial (RCT) cohort has been met. Primary endpoints are change in mean 24-hour ambulatory systolic blood pressure from baseline to 8 weeks (TARGET BP OFF-MED) and 3 months (TARGET BP I) post-procedure.

Conclusion The TARGET BP trials are the first large-scale, international, randomized trials aimed to investigate the safety and BP lowering efficacy of a novel RDN method, with perivascular alcohol delivery using the Peregrine Kit. (Am Heart J 2021;239:90–99.)

Introduction

Hypertension is the leading global cause of death and disability[1], yet the prevalence of treatment and control of blood pressure among hypertensive individuals has plateaued, if not modestly declined.[2,3] The persistence of uncontrolled hypertension has therefore introduced the opportunity for device-based therapies as an alter-

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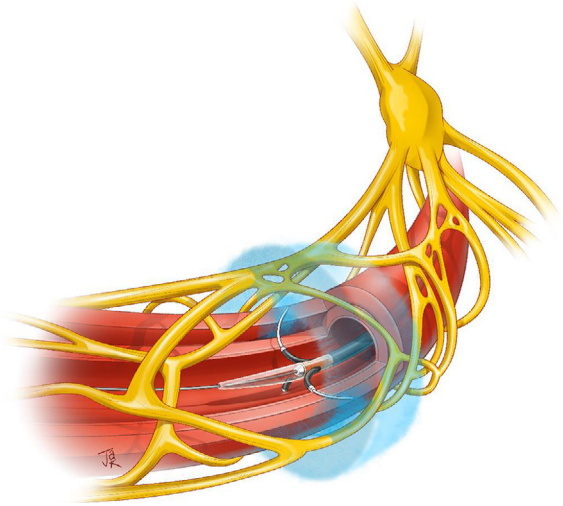
Figure 1



The Peregrine Catheter. The device accesses the sympathetic nerves by puncturing of the vessel wall with the 3 needles. Medical Illustration by Justin A. Klein, CMI 2020.

native to conventional medication therapies. Catheter-based renal denervation (RDN) has been evaluated in patients with uncontrolled hypertension, both in the presence and absence of antihypertensive medications. Specifically, recent sham-controlled trials utilizing radiofrequency and ultrasound energy have demonstrated the blood pressure lowering efficacy and safety of these methods.[4,5,6,7]

Alcohol has been used as an agent to chemically ablate nerves in a variety of clinical indications, secondary to its neurolytic activity. Thus, making this approach attractive for RDN in hypertension.[8,9,10,11,12,13,14] As a novel RDN method, the Peregrine System Infusion Catheter is delivered into the main and large accessory renal arteries under fluoroscopic guidance to ensure correct positioning. Alcohol is infused directly into the perivascular space (adventitia and periadventitial space) via three micro-needles supported by "guide tubes." (see Figure 1). Such a method permits deep (up to 8 mm from the intimal surface) and circumferential delivery of alcohol to the perivascular space to allow reproducible renal sympathetic nerve denervation, which has been demonstrated in a porcine model.[15,16]

First-in-man and open-label clinical trials have demonstrated the clinical safety and feasibility of this chemical approach to RDN using the Peregrine Catheter.[17,18] The safety profile of alcohol mediated RDN in these two studies was good with low incidence of adverse effects. Notably, the absence of nephrotoxic or systemic effects[17] and absence of any periprocedural major vascular complications or major bleeding, acute kidney injury or death within 1 month of the RDN procedure in 43/45 (96%) of subjects.[18] The prospective, single-arm, open-label, multicenter Peregrine Post-Market trial demonstrated that the injection of 0.6 mL of alcohol per artery can induce clinically meaningful reductions in 24-hour ambulatory and office blood pressure.[18] The encouraging results from these initial clinical trials established the foundation for the ongoing TARGET BP I (NCT02910414) and TARGET BP OFF-MED (NCT03503773) trials. These two prospective, randomized, assessor-blinded, sham procedure-controlled, multicenter trials are designed to assess the efficacy and safety of alcohol-mediated RDN in uncontrolled hypertensive subjects either in the absence of antihypertensive medication (TARGET BP OFF-MED trial) or prescribed 2-5 antihypertensive medications (TARGET BP I trial). Moreover, the pivotal TARGET BP I trial will explore the impact of alcohol-mediated RDN on subject self-reported health status, including quality of life (QoL) and sleep behavior. Enrollment is closed in TARGET BP OFF-MED and ongoing in TARGET BP I, with primary endpoint results of the TARGET BP OFF-MED trial expected later in 2021 and for the TARGET BP I trial in 2023.

Methods

The peregrine system kit

The Peregrine System Kit is an investigational combination product, consisting of a device component, the Peregrine Catheter, and dehydrated alcohol, United States Pharmacopeia (USP), as the drug component. The mode of action and the design of the Peregrine Catheter have been described previously.[15,17,19] Specifically, the Peregrine Catheter is designed to accommodate the typical range of renal artery diameters (4-7 mm) when deployed and intended to deliver alcohol to the perivascular area of the renal arteries to ablate afferent and efferent sympathetic nerves. Three equally spaced, distal, deployable micro-needles (0.008"), housed inside individual guide tubes, are retractable to facilitate introduction and removal of the catheter. The micro-needles and guide tubes are radiopaque for fluoroscopic visibility. Depth of needle penetration is fixed at ˜3.5 mm deep to the intimal surface (tip of deployed guide tubes) to optimize the location of alcohol delivery directly to the adventitia of the artery, and to enhance device safety. When deployed, all three needles simultaneously inject alcohol into the perivascular space. Per artery, one injection is performed. The catheter is intended for the treatment of vessels 4 to 7 mm in diameter and is compatible with ≥7 Fr guide catheters up to 55 cm in length. The Peregrine Catheter is 510(k) cleared in the US and CE marked in Europe.

The drug component, alcohol, does not comprise any other chemical compounds like co-solvents, buffers, ex-

cipients or other additives. It is administered as a single direct infusion of 0.6 mL per renal artery, with up to 1.2 mL per side (in case one additional accessory artery is treated) and a maximum dose of 2.4 mL per subject. Alcohol induces injury to cells by dehydration and precipitation of cell protoplasm and denaturation of proteins. When injected near nerve tissues, it produces neuritis and nerve degeneration (neurolysis). No receptor binding or metabolic interactions are required to achieve the full effect of this neurolysis. The hygroscopic nature of alcohol allows for dilution as it is distributed along the perivascular space when administered through the catheter.

Trial design

Target BP OFF-MED

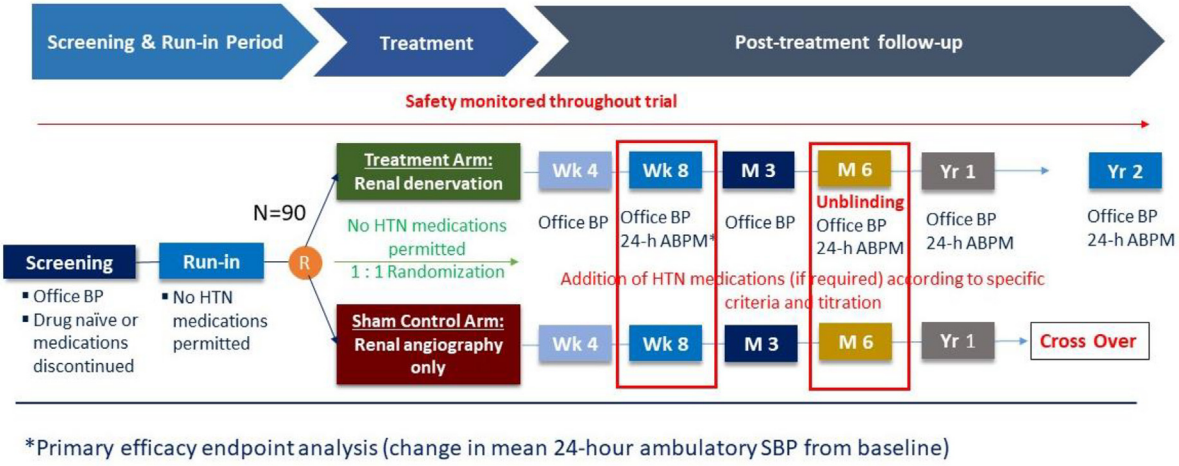
The phase 2 blinded, sham procedure-controlled TARGET BP OFF-MED trial has been initiated in approximately 28 centers in the US and Europe. Subjects with a documented history of uncontrolled hypertension who are taking 0, 1, or 2 antihypertensive medications are recruited. The Peregrine Kit is tested in a population of hypertensive subjects receiving no antihypertensive medications for a period of 12 weeks (4 weeks prior to the procedure [run-in period] and 8 weeks post-procedure). Similar to pharmaceutical trials with regulatory oversight, the purpose of studies with a drug washout or drug naïve patient population is to confirm the biological proof of principle using this particular method of RDN in the absence of confounding effect related to medications. At the end of the run-in period, all subjects undergo diagnostic renal angiography. Patients are blinded to treatment status by sensory deprivation (e.g., blindfold and earphones) and sedation. If anatomically suitable renal artery anatomy is confirmed, the subjects are randomized (1:1) in the catherization laboratory to receive either RDN using the Peregrine Kit with alcohol (0.6 mL per treated renal artery, maximum dose of 2.4 mL per patient) infused through the Peregrine Catheter (RDN arm) or diagnostic renal angiography only (sham control arm) (Figure 2). If clinically indicated, reinstatement of antihypertensive medication will be permitted at 8 weeks after the procedure according to pre-specified criteria and titration scheme (Supplemental Materials). Unblinding will take place after the last subject has completed their 6-month follow-up visit. Long-term safety of the procedure will be assessed through to 2 years, as subjects return for follow-up visits at 4 and 8 weeks, 3 and 6 months, and 1- and 2-years post-randomization.

Target BP I

The phase 3 pivotal, blinded, sham procedure-controlled TARGET BP I trial, with approximately 100 centers in the US and Europe, comprises 2 sequential cohorts: the Randomized Controlled Trial (RCT) cohort and the safety cohort (Figure 3). The study has been designated as pivotal as it is powered for the primary efficacy endpoint. The RCT cohort is designed to assess whether RDN using the Peregrine Kit provides additive blood pressure-lowering effects in subjects whose blood pressures remain elevated despite prescription of a stable regimen of 2 to 5 antihypertensive medications. Following screening based on medical history, office blood pressure and renal artery anatomy by magnetic resonance angiography [MRA] or computed tomography angiography [CTA], eligible subjects who complete informed consent will enter a 4-week run-in period during which they will remain on a stable regimen of antihypertensive medications. Similar to TARGET BP OFF-MED, at the end of the run-in period, up to 300 subjects will be randomized (1:1) in the catherization laboratory to receive either RDN or only a diagnostic renal angiography (sham procedure). Subjects will continue on the same regimen of antihypertensive medications with changes permitted only for safety reasons during the first 3 months after the randomization. After 3 months, changes in antihypertensive medications are allowed according to specified criteria and a proposed titration scheme (Supplemental Materials). Follow-up visits are performed at 4 and 8 weeks, 3, 4, 5, and 6 months, and 1, 2 and 3 years post-procedure. Health care providers and research staff during the follow-up phase are blinded to the subjects' treatment assignment. Following enrollment completion in the RCT cohort, and upon unblinding of the data (when the last subject has reached the 6-month follow-up), and assuming the primary efficacy endpoint of clinically meaningful blood pressure lowering effect at the 3-month time point has been met, the trial will transition to a single-arm, open-label phase of consecutive subjects fulfilling the same enrollment criteria and treated with RDN using the Peregrine Kit ('safety cohort', N = 300). This open-label cohort is intended to collect additional safety and efficacy data (reaching a total of approximately 450 subjects receiving RDN in both the RCT and safety cohorts). Follow-up in the safety cohort will be performed up to 1 year with visits at 30 days, 8 weeks, 3 and 6 months, and 1 year.

In both trials, investigators will implement a rescue therapy approach, as needed, to maintain a blood pressure within the required (safe) values. From the start of the run-in period through the Week 8 visit (TARGET BP OFF-MED) or the Month 3 visit (TARGET BP I), subjects with systolic blood pressure (SBP) $\geq$180 mm Hg or diastolic blood pressure (DBP) $\geq$110 mm Hg will return for a repeat of this measurement within 2 days following the initial value. If the repeated BP measurement confirms a SBP $>$180 mm Hg or diastolic blood pressure (DBP) $\geq$110 mm Hg, with symptoms or end-organ damage secondary to uncontrolled hypertension, the subject will receive rescue medication at the investigator's discretion. If a subject is taking antihypertensive medication (TARGET BP OFF-MED) or changes his/her regimen of antihypertensive medication (TARGET BP I) during the

Figure 2



TARGET BP OFF-MED trial design.

run-in period but still wishes to enter the trial, one restart of the run-in period is possible. If a subject in the TARGET BP I trial has a symptomatic decrease of the office SBP, or an asymptomatic office SBP of <90 mm Hg, a repeat of this measurement is done within 2 days following the initial value. If this repeat shows a value of ≤90 mm Hg, antihypertensive medication can be decreased.

Crossover from the sham control arm to the RDN arm is allowed in both trials, following assessment of the interim results at 6 months from all subjects, trial unblinding, after the subject has completed the 1-year follow-up visit, and continues to have uncontrolled hypertension. A new written informed consent will be required, as well as re-screening assessments and eligibility checks. Subjects who crossover will undergo safety follow-up to 6 months and 1 year after the procedure in the TARGET BP OFF-MED and TARGET BP I trial, respectively.

Trial population

Target BP OFF-MED

Subjects, aged 18–80 years, are eligible to participate in the TARGET BP OFF-MED trial if they have a documented history of hypertension in the absence of medications (mean office SBP ≥140 and ≤180 mm Hg and mean office DBP of ≥90 mm Hg) or uncontrolled hypertension on 1-2 prescribed antihypertensive medications Table 1 (mean office SBP ≥120 and ≤180 mm Hg) and are willing to adhere to the no-medication regimen for at least 12 weeks (4-week run-in period and 8-week post-treatment period). At the end of the run-in period, all subjects must have a mean office SBP ≥140 and ≤180 mm Hg and a mean office DBP of ≥90 mm Hg with mean 24-hour ambulatory SBP ≥135 and ≤170 mm Hg.

Target BP I

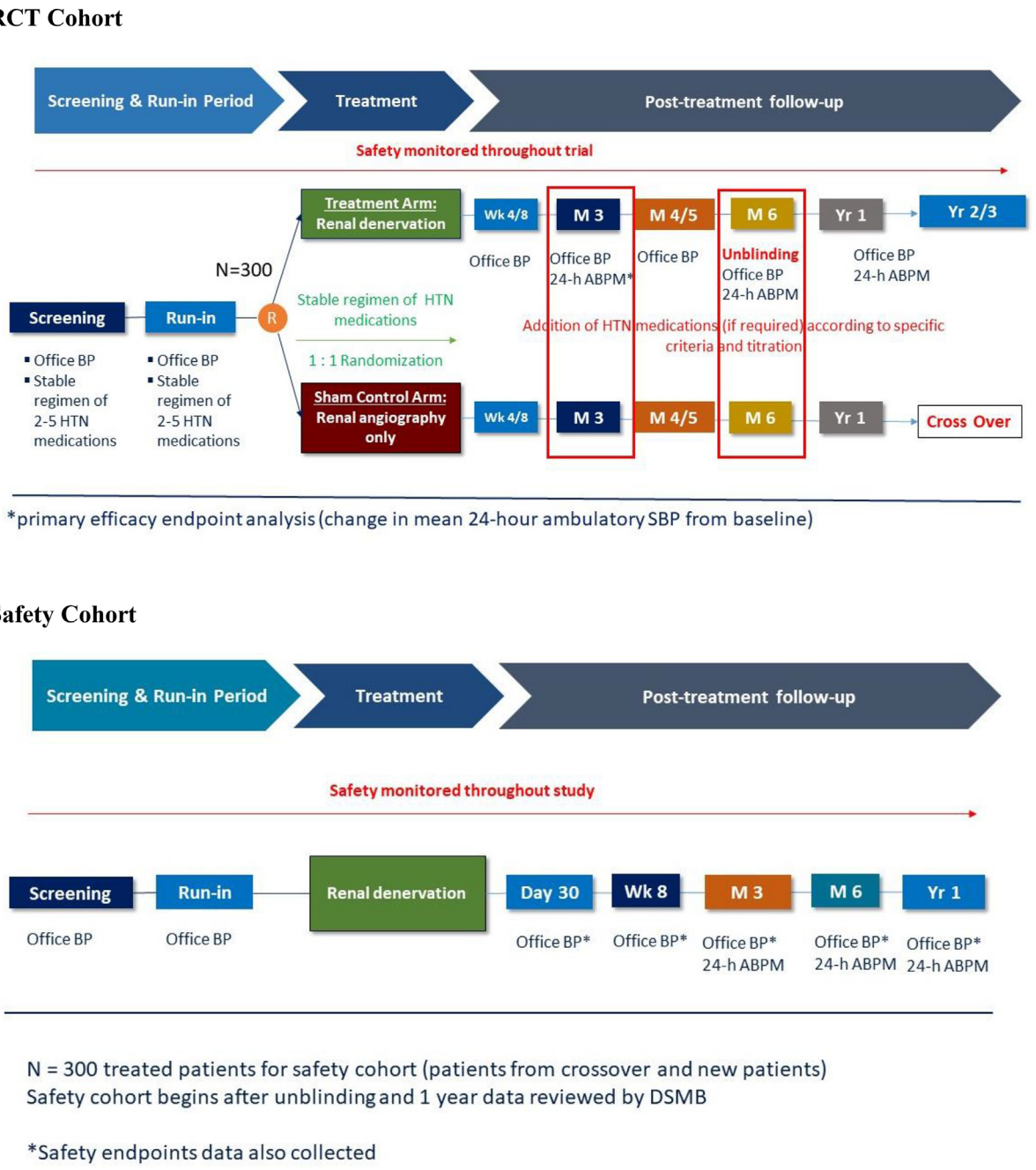
In the TARGET BP I trial, subjects aged 18–80 years have a history of uncontrolled hypertension as confirmed by office SBP ≥150 and ≤180 mm Hg, office DBP ≥90 mm Hg, and mean 24-hour systolic ambulatory blood pressure monitoring (ABPM) ≥135 and ≤170 mm Hg. They must be on a stable medication regimen of 2-5 antihypertensive medications Table 1, two of which must be at least at 50% of their maximally labeled dose prior to the planned procedure. All subjects must currently be taking, or have documentation that they cannot tolerate, a diuretic. In the case of hydrochlorothiazide and chlorthalidone, doses should be 25 mg daily. In subjects on two medications, one should be an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

Inclusion and exclusion criteria are fully described in the Supplemental Materials. The first subjects in the TARGET BP OFF-MED and TARGET BP I trials were enrolled in January 2019 and May 2019, respectively. As of 14 December 2020, 349 and 96 subjects have been enrolled and randomized, respectively, in the TARGET BP OFF-MED trial and 231 and 39 subjects have been enrolled and randomized, respectively, in the TARGET BP I trial.

Run-in, randomization and blinding

During the 4-week run-in period, a safety visit takes place approximately 2 weeks before the procedure, and further trial assessments and a final check of eligibility criteria, including a 24-hour ABPM, are performed approximately 1 week before the procedure (baseline

Figure 3



TARGET BP I trial design.

visit). The baseline 24-hour ABPM is only performed if the office blood pressure measurement at that time point meets the inclusion criteria. Subjects who continue to be eligible at the end of the run-in period are randomized to either the RDN arm or the sham control arm after renal angiography as detailed above. Randomization, stratified by trial site, is performed centrally using an interactive web response system (IWRS) when the subject is in the catherization laboratory on the day of the procedure, after the subject has been blinded and has undergone diagnostic renal angiography for confirmation of anatomical eligibility. In both trials, subjects in the sham

control arm undergo diagnostic renal angiography only instead of the RDN procedure and remain in the catherization laboratory/recovery room for a time equal to that for subjects in the RDN arm, in order to avoid any potential unblinding of the subject. The subject, the investigator (hypertension specialist) and other designated members of the trial site team who perform the trial assessments (including screening and follow-up assessments, in particular the office blood pressure, ABPM and safety assessments) are blinded to the subject's treatment assignment. The physician performing the procedure (interventionalist), catherization laboratory staff and dedicated research personnel are unblinded. Subjects receive sedation, are blindfolded, and wear headphones playing music, to minimize the possibility of inadvertent unblinding by overhearing conversations by catherization laboratory staff during the procedure. As an assessment of the effectiveness of the blinding procedure, subjects are asked post-procedure to complete a questionnaire to determine their perception of which treatment they think they received (RDN or sham control).

Renal denervation and sham procedure

All subjects, either in the RDN arm or the sham control arm, receive sedation and analgesia. The RDN procedure using the Peregrine Catheter has been described previously.[18] The entire procedure, with RDN of both main renal arteries, and including up to one additional renal accessory artery on each side (as applicable) is performed in a single procedure. There are no dose titrations or adjustments of the 0.6-mL alcohol dose for any subject. To ensure the safety of the subject, the procedure (including diagnostic renal angiography and RDN) is performed by a trained physician according to the Peregrine Catheter instructions for use and detailed training materials. All procedures are attended by company proctors supervising the procedure. At the end of the procedure, compression or a closure device is applied to obtain hemostasis at the access site.

Efficacy, safety, and quality of life assessments

Office blood pressure is taken in a set of three or more measurements, separated by approximately 2 minutes, using the same cuff. Additionally, the subject is given a portable automated ABPM device and instructions for the recording of ambulatory blood pressure over 24 hours. ABPM data are sent for evaluation by the independent, blinded core laboratory. For all blood pressure measurements, the same arm as used at screening or baseline is used at subsequent follow-up visits. Office blood pressure and ABPM measurements are consistent with the EMA guidelines on the clinical investigation of medicinal products in the treatment of hypertension for the management of arterial hypertension.[20] Blood and urine samples are collected with subjects' awareness to survey compliance regarding the use/non-use of antihypertensive medications and are sent for central evaluation by the independent, blinded core laboratory Table 1.

Safety assessments include the standard measures as collection of adverse events and performing clinical laboratory tests, as well as tests specific to the procedure. The latter includes serum creatinine measurements and eGFR calculation to assess acute kidney injury and several imaging modalities such as renal duplex ultrasound [RDUS], MRA, CTA and/or renal angiography to assess longer term kidney effects and vascular safety.

Control of blood pressure and/or decreased number of antihypertensive medications may positively affect a patient's quality of life (QoL) and possibly their sleep behavior.[21] Accordingly, the TARGET BP I trial includes the non-invasive Pittsburgh Sleep Quality Index (PSQI) and 12-item Short Form Survey (SF-12) instruments in both the RDN and sham control arms in the RCT cohort.

Safety monitoring committees

For each trial, an independent and unblinded Data Safety Monitoring Board (DSMB) reviews the clinical data periodically over the course of the trial, including at the time of interim analysis to provide advice on the safety of the subjects. It also provides independent assessment of the ongoing scientific validity of the trial. Both trials will be unblinded for the analysis at 6 months. At this time, the DSMB will assess or make recommendations on the suitability of the crossover/further enrollment in the safety cohort. Specifically, the DSMB will assess the safety data and demonstration of efficacy with the presence of a clinically meaningful reduction in SBP, defined as a decrease of at least 5 mm Hg compared with baseline, as assessed by 24-hour ABPM. Additionally, a blinded Clinical Events Committee (CEC) reviews and adjudicates all treatment-emergent serious adverse events (SAEs) and potential major adverse events (MAEs) identified by the investigator, regardless of the investigator's assessment of relationship to the investigational product.

Statistical methods

Endpoints

The primary efficacy endpoint is the change in mean 24-hour ambulatory SBP from baseline to 3 months (TARGET BP I) or 8 weeks post-procedure (TARGET BP OFF-MED). All other endpoints, either efficacy or safety, are secondary or exploratory. Endpoints for both trials are listed in the Supplemental Materials. All efficacy and safety endpoints in the TARGET BP I trial are the same for both the RCT cohort and the safety cohort. Additionally, in the safety cohort, the change in mean 24-hour ambulatory SBP from baseline to 3 months post-procedure in control subjects who crossed over from the RCT cohort will be compared with their change from baseline to 3 months after the original sham procedure (paired analysis).

Table 1. Overview of the TARGET BP I and TARGET BP OFF-MED Trials

Phase	Country	Title	Design	Dosing Regimen	Population	(Planned) Enrollment
TARGET BP I						
3 (pivotal)	US UK Germany France Sweden Austria Belgium Netherlands Ireland Monaco Switzerland	A pivotal, multicenter, blinded, sham procedure-controlled trial of renal denervation by the Peregrine System Kit, in subjects with hypertension	Randomized, blinded, parallel-group, sham procedure-controlled, with 2 sequential cohorts	RDN or renal angiography only	Male or female subjects, aged ≥18 and ≤80 years, with uncontrolled hypertension who are on a stable medication regimen of 2-5 antihypertensive medications	~ 900 subjects, in order to randomize (1:1) ~ 300 subjects in the RCT cohort (150 per arm) and ~ 650 subjects, in order to treat ~ 300 subjects in the safety cohort
TARGET BP OFF-MED						
2 (proof-of-concept)	Germany Belgium UK France Netherlands Ireland US	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	Randomized, blinded, parallel-group, sham procedure-controlled	RDN or renal angiography only	Male or female subjects, aged ≥18 and ≤80 years, with uncontrolled hypertension who are taking no, 1 or 2 antihypertensive medications and are willing to take no medication for at least 12 wk	349 subjects enrolled* 96 subjects randomized (1:1)*

RCT = randomized controlled trial; RDN = renal denervation

*As of 14 December 2020.

Sample size considerations

The TARGET BP I trial is powered for the primary efficacy endpoint. Assuming a mean difference in mean 24-hour ambulatory SBP between RDN procedure and sham control of 6 mm Hg (δ1) with standard deviation per group of 16 mm Hg, then 300 evaluable subjects in the RCT cohort would provide 90% power to detect this difference at the two-sided alpha level of 0.05. Subjects will be enrolled into the subsequent safety cohort until the maximum 450 subjects treated with the Peregrine Kit in both the RCT and safety cohorts is reached.

Unlike the TARGET BP I trial, the TARGET BP OFF-MED trial is designed as a proof-of-concept trial and is not formally powered for the primary efficacy endpoint but has the purpose of determining whether there is an adequate treatment effect to proceed to a pivotal study. A total of 96 subjects (48 per arm) were randomized to attain 80 evaluable subjects.

Data analyses

In each trial, the primary efficacy endpoint will be compared between treatment groups using Analysis of Covariance, adjusted for the baseline value. The null hypothesis to be tested is that there is no difference in the change in 24-hour ambulatory SBP between RDN and sham control. The type I error rate for rejecting the null hypothesis is set at a two-sided alpha level of 0.05. The primary analysis for the TARGET BP I trial will be conducted using multiple imputations via the Markov Chain Monte Carlo (MCMC) method to account for missing observations at the primary analysis time point. For TARGET BP OFF-MED, the primary analysis will include only available data. For the primary analysis, subjects receiving escape medications will have their data included as measured as part of the intent to treat approach. Various sensitivity analyses will be conducted for subjects receiving escape medications, including 1) imputing their last value prior to receiving medication, 2) removing those subjects from the analysis, and 3) a hierarchical modeling approach counting those subjects receiving escape medication as failures in the first tier, followed by comparison of change in blood pressure in the second and final tier.[22,23]

Subgroups based on the following key demographic, medical history and clinical characteristics will be assessed for the primary efficacy endpoint: age, race, gender, region, requiring a change of antihypertensive medi-

cation post-procedure, baseline ambulatory SBP and DBP, baseline eGFR, changes in eGFR. Additionally, for TARGET BP I, the following will be explored: type II diabetes mellitus, body mass index, baseline number of antihypertensive medications, renal accessory artery treatment, baseline heart rate, baseline 24-hour ABPM, adherence to antihypertensive medications assessed through blood and urine sample testing during the 3-month follow-up.

For TARGET BP I, formal testing of secondary efficacy endpoints will proceed hierarchically if, and only if, the primary efficacy endpoint is met. In TARGET BP OFF-MED, analyses of secondary efficacy endpoints are considered supportive. The key safety endpoint for both trials, the percentage of subjects with any MAE through 30 days post-procedure, will be displayed by treatment group, including the relative risk with 95% CIs. The 2 treatment groups will be compared using Fisher's exact test.

Interim analyses

For TARGET BP I, the primary efficacy endpoint analysis will be conducted for all subjects in the RCT cohort when the last subject has reached the 6-month follow-up and the trial is unblinded. These results will inform the appropriateness of the crossover after review and input by the DSMB and the plan to further enroll in the safety cohort.

For TARGET BP OFF-MED, a blinded 8-week interim analysis and an unblinded 6-month interim analysis are planned. The 8-week interim analysis including all available data through the 8-week follow-up, may be presented in an aggregate fashion (by treatment group) and will be assessed by the unblinded DSMB in accordance with the DSMB charter. The individual treatment assignments will remain blinded at this time. The second interim analysis will include all available data through 6 months. The trial will be unblinded for analysis at this time. The 6-month interim analysis results will inform the appropriateness of the crossover.

Discussion

The TARGET BP trials are the first randomized, blinded, sham-controlled trials to assess the safety and efficacy of chemical RDN using alcohol as the neurolytic agent. The TARGET BP OFF-MED trial aims to confirm the biologic proof of principle of alcohol-mediated RDN and will inform treatment of uncontrolled hypertension in the absence of antihypertensive medication. The TARGET BP I trial is intended to confirm the efficacy and safety of RDN with the Peregrine Kit among patients with uncontrolled blood pressure taking 2-5 antihypertensive medications.

Both trials use an invasive placebo control, which helps to assure the blinding of the trial subjects. Randomization and blinding are considered important design components for trials where there are potentially issues of bias.[24,25,26] Use of renal angiography in the sham control subjects is now standard in RDN clinical trials, and is still considered a critical design element for trials of device-based therapies in patients with hypertension.[4,5,6,25] Conscious sedation is used to ensure that the sham control procedure is as similar as possible to the RDN procedure.

In the TARGET BP OFF-MED trial, the absence of antihypertensive medications through ascertainment of the primary endpoint at 8 weeks should minimize the potential confounding effect of antihypertensive medication use on the efficacy assessment. In the absence of antihypertensive medications, the TARGET BP OFF-MED trial should allow a more objective evaluation of the blood pressure-lowering effects of RDN and follows international recommendations for trial design.[24,25,26]

Chemical RDN represents an alternative approach to renal nerve ablation, and contrasts in some ways with "energy-based" methods of denervation, such as with radiofrequency (RF) or ultrasound (thermal) ablation techniques. Radiofrequency energy was used in the first systems for RDN.[27,28,29,30] An alternative, balloon-based technology delivers ultrasound (thermal) energy as a means to ablate the renal sympathetic nerve fibers as they pass alongside the renal arteries. Both RF and ultrasound use energy passed through the arterial wall to thermally ablate the surrounding renal sympathetic nerves. These approaches have different characteristics, related to the depth and circumferential patterns of renal nerve ablation. Alcohol-mediated neurolysis in the perivascular area of renal arteries offers potential benefits compared with RF energy.[16] The delivery of site-specific, microvolumes of alcohol contributes to the safety and predictability of the procedure by minimizing damage to intima, media, and tissues surrounding the artery.[16] The duration of the procedure is relatively short since the alcohol infusion, using the Peregrine Catheter requires only 1-2 minutes of drug delivery per artery. The Peregrine device is only deployed once in each treated renal artery. Accordingly, this may translate into lessened radiation exposure and contrast use. Chemical RDN necessitates only a catheter with alcohol, with no need for capital equipment, which may improve user-friendliness and possibly reduce costs.

In the TARGET BP OFF-MED trial, the planned duration of participation for each subject is approximately 26 months with, in case of crossover, a maximum duration of approximately 33 months for subjects in the sham control arm. In the TARGET BP I trial, each subject in the RCT cohort will be included in the trial for approximately 40 months. In case of crossover to the safety cohort, the duration of the trial may vary from approximately 28 to 56 months for subjects in the sham control arm. Subjects who enter only into the safety cohort will be included in the trial for approximately 16 months. Fur-

ther, the TARGET BP I and TARGET BP OFF-MED trials will collect important additional information on the vascular and renal safety profile of alcohol-mediated renal denervation.

Conclusion

The TARGET BP trials are underway, with the TARGET BP OFF-MED trial now nearing the completion of randomization. Trial completion is expected in 2023 for TARGET BP OFF-MED and in 2024 for TARGET BP I. Together, these randomized, international clinical trials will provide important insights relevant to the safety and efficacy of chemical RDN with alcohol using the Peregrine Kit, as a means to treat hypertension.

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Disclosure

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.05.015.

References

1. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217–23.
2. Egan BM, Li J, Hutchison FN, Ferdinand KC. Hypertension in the United States, 1999 to 2012: progress toward Healthy People 2020 goals. Circulation 2014;130:1692–9.
3. Muntner P, Carey RM, Gidding S, et al. Potential US Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. Circulation 2018;137:109–18.
4. 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 randomized, sham-controlled, proof-of-concept trial. Lancet 2017;390:2160–70.
5. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet 2018;391:2335–45.
6. Kandzari DE, Bohm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet 2018;391.
7. Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. Lancet 2020 S0140-6736(20)30554-7.
8. Koyyalagunta D, Engle MP, Yu J, et al. The effectiveness of alcohol vs phenol based splanchnic nerve neurolysis for the treatment of intra-abdominal cancer pain. Pain physician 2016;19:281–92.
9. Viel EJ, Perennou D, Ripari J, et al. Neurolytic blockade of the obturator nerve for intractable spasticity of adductor thigh muscles. European journal of pain 2002;6:97–104.
10. Kocabas H, Salli A, Demir AH, et al. Comparison of phenol and alcohol neurolysis of tibial nerve motor branches to the gastrocnemius muscle for treatment of spastic foot after stroke: a randomized controlled pilot study. Eur J Phys Rehabil Med 2010;46:5–10.
11. O'Toole TM, Schmulewitz N. Complication rates of EUS-guided celiac plexus blockade and neurolysis: results of a large case series. Endoscopy 2009;41:593–7.
12. Bhatnagar S, Joshi S, Rana SP, et al. Bedside ultrasound-guided celiac plexus neurolysis in upper abdominal cancer patients: a randomized, prospective study for comparison of percutaneous bilateral paramedian vs unilateral paramedian needle insertion technique. Pain Pract 2014;14:E63–8.
13. Leblanc JK, Leblanc JK, Rawl S, et al. Endoscopic ultrasound-guided celiac plexus neurolysis in pancreatic cancer: a prospective pilot study of safety using 10 mL vs 20 mL alcohol. Diagn Ther Endosc 2013.
14. Kambadakone A, Thabet A, Gervais DA, et al. CT-guided celiac plexus neurolysis: a review of anatomy, indications, technique,

and tips for successful treatment. Radiographics 2011;31:1599–621.
15. Fischell TA, Vega F, Raju N, et al. Ethanol-mediated perivascular renal sympathetic denervation: preclinical validation of safety and efficacy in a porcine model. EuroIntervention 2013;9:140–7.
16. Bertog S, Fischell TA, Vega F, et al. Randomised, blinded and controlled comparative study of chemical and radiofrequency-based renal denervation in a porcine model. EuroIntervention 2017;12:e1898–906.
17. Fischell TA, Ebner A, Gallo S, et al. Transcatheter Alcohol-Mediated Perivascular Renal Denervation With the Peregrine System: First-in-Human Experience. JACC Cardiovasc Interv 2016;9:589–98.
18. Mahfoud F, Renkin J, Sievert H, et al. Alcohol-mediated renal denervation using the Peregrine System Infusion Catheter for treatment of hypertension. JACC 2020;13:471–84.
19. Fischell TA, Fischell DR, Ghazarossian VE, et al. Next generation renal denervation: chemical "perivascular" renal denervation with alcohol using a novel drug infusion catheter. Cardiovasc Revasc Med 2015;16:221–7.
20. Guideline on clinical investigation of medicinal products in the treatment of hypertension.European Medicines Agency. 2016. Available at : https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-hypertension-revision-4_en.pdf Last accessed October 2020.
21. Schmieder RE, Jumar A, Fronk EM, et al. Quality of life and emotional impact of a fixed-dose combination of antihypertensive drugs in patients with uncontrolled hypertension. J Clin Hypertens 2017;19:126–34.
22. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Statistics in medicine 1999;18:1341–54.
23. Pocock SJ, Ariti CA, Collier TJ, et al. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J 2012;33:176–82.
24. Mahfoud F, Böhm M, Azizi M, et al. Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design. Eur Heart J 2015;36:2219–27.
25. Mahfoud F, Schmieder RE, Azizi M, et al. Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: state of the art and considerations for the future. Eur Heart J 2017;38:3272–81.
26. Mahfoud F, Azizi M, Ewen S, et al. Proceedings from the 3rd European Clinical Consensus Conference for clinical trials in device-based hypertension therapies. Eur Heart J 2020;41:1588–99.
27. Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 2010;376:1903–9.
28. Krum H, Schlaich MP, Sobotka PA, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet 2014;383:622–9.
29. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension,(SYMPLICITY HTN-3). N Engl J Med 2014;370:1393–401.
30. Kandzari DE, Bhatt DL, Brar S, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur Heart J 2015;36:219–27.