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

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The current proof-of-concept study has been designed to assess the efficacy and safety of the Peregrine Kit in the treatment of subjects with hypertension, when discontinued from their antihypertensive medications. This will be an *off medication*...

Ethical review	Approved WMO
Status	Completed
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON54821

Source
ToetsingOnline

Brief title
The TARGET BP OFF-MED Trial

Condition

- Vascular hypertensive disorders

Synonym
High blood pressure, hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Ablative Solutions Inc
Source(s) of monetary or material Support: Ablative Solutions. Inc

Intervention

Keyword: Blinded Study, Hypertension, Non Medication use, Renal Denervation

Outcome measures

Primary outcome

The primary efficacy endpoint is defined as the change in mean 24-hour ambulatory SBP from baseline to 8 weeks post-treatment.

Secondary outcome

The secondary efficacy endpoints are defined as follows:

• 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 ambulatory SBP and DBP from baseline to 8 weeks, 6 months, and 1 year

• Change in mean nighttime 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 SBP of <140 mmHg and >=90 mmHg; see Section 7.2.2)

• Compliance with not taking antihypertensive medications, as assessed by blood and urine testing, through the 8 week follow-up visit.

Secondary Safety Endpoints

Secondary safety endpoints are defined as follows:

• 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:

o All-cause death

o End-stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m2 or need for renal replacement therapy)

o Significant embolic event resulting in end-organ damage or requiring intervention to prevent it

o 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)

o Major bleeding related to renal denervation within the renal arteries, or related to the Peregrine Catheter when in the body (per bleeding definition in Definitions section)

o 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 (see Definitions section), as confirmed by renal function blood test,
or (ii) percutaneous intervention.

o Hypertensive crisis (hypertensive emergency only)

o Hypotensive crisis

o 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 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).

Study description

Background summary

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.

Study objective

The current proof-of-concept study has been designed to assess the efficacy and safety of the Peregrine Kit in the treatment of subjects with hypertension, when discontinued from their antihypertensive medications. This will be an *off medication* study to confirm the basic
hypothesis that renal denervation using the Peregrine Catheter and alcohol, as a neurolytic agent, lowers blood pressure in subjects with hypertension without treatment. Exclusion of all antihypertensive medications, for 4 weeks before the procedure through to the time point of the
primary efficacy endpoint at 8 weeks, will remove the confounding effects of these medications on the efficacy assessments. Long-term follow-up to 2 years post-treatment will provide a thorough long term assessment of safety.

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 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

Intervention

In this protocol, *treatment* is a general term that refers to the renal

denervation procedure (i.e. Treatment Arm) or control renal angiography (i.e. Sham Control Arm).
Each subject will be randomized to either the Treatment Arm or Sham Control Arm.
Subjects who are in the Sham Control Arm may be offered the possibility to undergo renal denervation in a crossover phase

Treatment Arm:
The test product in this study is a co-packaged combination product, the Peregrine Kit, which includes the Peregrine Catheter (CE marked) and alcohol for injection. The catheter will be used to deliver a dose of 0.6 mL alcohol by direct infusion to the perivascular space of each renal artery in a single treatment session (i.e. a target dose of 1.2 mL). The 2 main renal arteries (1 on each side) will be treated. However, the treating physician is permitted to treat up to 1 additional accessory renal artery on each side (during the same treatment session) as well (depending on individual subject anatomy). Thus, the planned maximum total dose per subject is 4 x 0.6 mL = 2.4 mL.

Sham Control Arm:
The sham control in this study is renal angiography only. There will be no insertion of the Peregrine Catheter and no alcohol infusion (i.e. no renal denervation).
For subjects who are in the sham control arm, the amount of contrast used during the renal angiography will not exceed 100 mL.

Study burden and risks

The burden and risks of the subjects are different in both arms. Subjects in the procedure arm will have more- and higher burden and risks based on the fact that they will have a renal denervation while the subject in the control arm will not have the denervation, but will have to undergo a renal angiography.

But the investigator and sponsors of the study are providing mitigation for every potential risk, and after assessing the risks vs. the benefits, have concluded that the potential benefits outweigh the known and potential risks associated with the participation in this study. (see protocol page 34 - 37).

Potential Risks

Subjects in this study will be exposed to potential risks and burden as follows:
1. As part of this study, subjects must discontinue their antihypertensive medications (if on 1 or 2 medications) for at least 4 consecutive weeks prior to the procedure (run-in period), and 8 weeks after the procedure.
2. The exposure to risks related to the percutaneous procedure and the use of a novel catheter and the infusion of a drug in a location that has not been previously approved.
3. Exposure to risks associated with renal angiography (injection of contrast

without receiving treatment)
4. The exposure to radiation and contrast and any risks associated with sedation while not receiving the treatment
5. The burden of having a blood pressure monitor and a cuff around the arm for 24-hours, with blood pressure measurements taken every 30 minutes.

Potential Benefits

1. While the subjects are not taking their antihypertensive medications, they will be on a very close medical monitoring to ensure their safety.
2. If the renal denervation is ultimately proven to be effective, the patients who are on 1 or 2 medications will have fewer risks associated with the administration of medications and their side effects or intolerance. In addition, there will be no concerns of non-compliance with taking the medications.
3. Although subjects in the sham group will not receive the potential benefit of the renal denervation, they will benefit from close medical monitoring and tests by their treating physicians to ensure their safety since they will also be without medications for 8 weeks after the procedure. These subjects will also be offered to receive the same treatment if they choose to, 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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

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:
o Have 3 office blood pressure measurements with a mean office SBP of >=140 mmHg and <=180
mmHg AND mean office DBP >=90 mmHg, and
o 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:
o Have 3 office blood pressure measurements with a mean office SBP of >=120 mmHg and <=180
mmHg, and
o 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 , 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.
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

1. Subject has a contraindication known for conventional percutaneous interventional procedures.
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. MRA/CTA examination and/or renal angiography) meeting one of the following criteria:
o Main renal artery that has a diameter of <4 mm or >7 mm and length of <5 mm
o 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.
o Renal artery stenosis >50% of the normal diameter segment (diameter stenosis, compared to the angiographically normal proximal or distal segment)
o 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)
o 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
o Previous renal denervation
o 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 orthostatic hypotension at baseline, 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.
7. Subject has Type 1 diabetes mellitus, or uncontrolled Type 2 diabetes mellitus (defined as hemoglobin A1c [HbA1c] >=9.0%). 8. Subject has an eGFR of <=45 mL/min/1.73 m2, based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; or is on chronic renal replacement therapy.
9. Subject has nephrotic syndrome. 10. 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.
11. Subject has a renal transplant, or is known to have a non-functioning kidney or unequal renal size 14. Subject has a history of myocardial infarction, unstable angina pectoris, or stroke/TIA within 6 months prior to the planned procedure.
12. 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).
13. 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.
14. If female, subject is pregnant or lactating at the time of enrollment or planning to become pregnant during the trial time period.
15. 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.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial

Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	20-11-2019
Enrollment:	50
Type:	Actual

Medical products/devices used

Generic name:	Peregrine System(TM) Infusion Catheter
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	20-05-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	18-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-000036-96-NL
ClinicalTrials.gov	NCT03503773
CCMO	NL66641.056.19

Study results

Date completed: 19-01-2024

Results posted: 07-08-2024

First publication
11-06-2024