Controlling And Lowering blood pressure with the MobiusHD device: STudying effects in A Randomized Trial.

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To determine the safety of the MobiusHD System and the efficacy of the MobiusHD device in lowering mean systolic 24-hour ambulatory blood pressure in subjects with resistant hypertension. The hypothesis is that mean systolic 24-hour ambulatory blood...

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

Summary

ID

NL-OMON47214

Source
ToetsingOnline

Brief title
CALM-START

Condition

- Vascular hypertensive disorders

Synonym
drug resistant high blood pressure, resistant hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Vascular Dynamics, Inc.
Source(s) of monetary or material Support: Vascular Dynamics;Inc.

Intervention

Keyword: Baroreflex, Blood pressure, Resistant hypertension

Outcome measures

Primary outcome

The primary efficacy endpoint is the difference in the change in mean systolic 24-hour ambulatory blood pressure - in subjects after antihypertensive medication washout - from baseline to 90 days post-randomization, between the treatment arm and the sham arm.

Secondary outcome

Secondary efficacy endpoints are differences in a) ambulatory and office blood pressure measurements (on and off medication), b) antihypertensive medication dosages, c) pathophysiology markers, and d) patient eand organ outcome markers from baseline through 180 days post-randomization, between the treatment and sham arms.

Safety endpoints are a) differences in the rate of serious adverse clinical events, including death, any stroke, carotid interventions, and/or myocardial infarction, from baseline to 30 days post-randomization, between the treatment and sham arms.

Study description

Background summary

Hypertension is a major worldwide problem, affecting one billion individuals globally. Among patients treated for hypertension, approximately 10% has

resistant hypertension, being unable to reach normotension despite treatment with at least 3 antihypertensive medications at optimal doses. These patients are at high risk of developing cardiovascular events. As these patients do not respond sufficiently to antihypertensive medication, there is a need for alternative strategies to lower blood pressure. One of the ways to achieve this, is by modulating the baroreceptor. The MobiusHD device is designed to do so.

The first in man (CALM-FIM) trial shows promising results on safety and efficacy. As a reasonable next step to further determine the efficacy of the MobiusHD device in lowering blood pressure, a randomized, double-blinded, sham-controlled trial in a small number of patients is necessary to eliminate the positive bias inherent in an early stage, uncontrolled, safety trial. Furthermore, to eliminate the confounding effects of antihypertensive medications on the efficacy of the MobiusHD device, effects will be evaluated in subjects after washout of such medications.

Study objective

To determine the safety of the MobiusHD System and the efficacy of the MobiusHD device in lowering mean systolic 24-hour ambulatory blood pressure in subjects with resistant hypertension. The hypothesis is that mean systolic 24-hour ambulatory blood pressure will be significantly lower in the treatment arm versus those in the sham arm.

Study design

A prospective, randomized, double-blind, sham-controlled, multi-center, post market study.

Intervention

Following initial eligibility screening, subjects will undergo wash out of all antihypertensive medications by stopping such medications for 14-28 days; the exact time depends on medication types. Subjects will be given information on symptoms that would require them to contact the study center during the washout period. Following washout, baseline ambulatory blood pressure and other markers will be measured. Subjects should be advised to resume their original antihypertensive medication regimen, at dosages determined based on the study guidelines and the presence of hypo-/hypertensive symptoms, and per the clinical acumen of the assessment team treating physician. Subjects will then be scheduled and admitted to the hospital for angiography. The angiography provides the final eligibility check. During this procedure, eligible subjects will be enrolled and randomized to either MobiusHD device implantation or sham implantation. The treatment and sham arms will be identically monitored at a follow-up visits until the 180 day time point.

At 90 days and 180 days post-randomization, the ambulatory blood pressure and other markers of all subjects will again be measured while the subjects are washed out of antihypertensive medications to determine the primary and secondary efficacy endpoints, respectively. In between these time points, the subjects will resume their prescribed antihypertensive medication regimens for safety. Medication adjustments will only be made if the subject is experiencing hypo-/hypertensive symptoms. Guidelines will be provided to the study centers. At 180 days post-randomization, the study will be unblinded.

Study burden and risks

The Controlling And Lowering Blood Pressure with the MobiusHD - First in Man (CALM-FIM) study demonstrated promising results on safety and in lowering BP in patients with resistant hypertension.

In brief, potential risks associated with this study are the risks of antihypertensive medication withdrawal (especially malignant hypertension with end organ damage); carotid device percutaneous implantation (especially stroke) and possible removal of the device; angiography (i.e. embolization, vessel complications and renal insufficiency); local anaesthesia; antiplatelet therapy (which can cause major bleeding); intravenous blood drawing; and radiation exposure.

Patients randomized to the intervention arm may benefit from the blood pressure lowering effect of MobiusHD implantation. Although this has not yet been confirmed in a well designed randomized trial. Patients in the sham arm may opt for MobiusHD implantation in the deferred treatment period.

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

Screening:
1. Aged 18-70 years;
2. Diagnosed with resistant hypertension;
3. A mean systolic 24-hour ambulatory blood pressure of 135-170 mmHg following at least 30 days on a stable antihypertensive medication regimen (no changes in medications or dose).;Baseline:
1. A mean systolic 24-hour ambulatory blood pressure of 135-170 mmHg after washout of all antihypertensive medications.

Exclusion criteria

Screening:
1. An inability to provide written informed consent;
2. Taking more than 4 antihypertensive medications;
3. Taking medications co-indicated for hypertension and a comorbidity that cannot be safely stopped for the antihypertensive medication washout periods (examples include beta-blockers) or taking other medications that cause hypotension (i.e. SGLT2 inhibitors for the treatment of diabetes mellitus) that cannot be safely switched/stopped;
4. Currently taking centrally acting agonists such as clonidine, moxonidine, or methyl dopa;
5. White coat hypertension, defined as >20% difference between an average of 3 consecutive systolic OBP measurements and mean systolic 24-hour ABP;
6. Patient with a history of hypertensive crisis in the past 6 months;
7. Known or clinically suspected baroreflex failure or autonomic neuropathy;
8. Known significant aortoiliac or common femoral artery disease that will prohibit safe femoral access, or determination upon femoral pulse assessment and examination of inguinal anatomy that femoral access is contraindicated;
9. Hypertension secondary to an identifiable cause other than treated sleep apnea (e.g.,

hyperaldosteronism, renal artery stenosis, pheochromocytoma, Cushing's syndrome, coarctation of the aorta, hyper- or hypothyroidism and intracranial tumor);
10. Treatable cause of hypertension including, but not limited to, improper BP measurement, volume overload and pseudotolerance (excessive sodium intake, volume retention from kidney disease, inadequate diuretic therapy), drug-induced or other causes (non-adherence, inadequate doses, inappropriate combinations, NSAIDs, COX-2 inhibitors, cocaine, amphetamines, or other drugs, sympathomimetics, oral contraceptives (confirmed cause of hypertension), adrenocortical steroids, cyclosporine, tacrolimus, erythropoietin, excessive licorice (including some chewing tobacco), ephedra, ma haung, bitter orange; and excessive alcohol intake;
11. Arm circumference >46 cm and/or BMI >=40 kg/m2;
12. Chronic atrial fibrillation, or intermittent atrial fibrillation with one or more episode(s) within the last twelve (12) months;
13. History of bleeding complications with dual antiplatelet therapy in the past, or has known uncorrected bleeding diathesis, or has history of Heparin Induced Thrombocytopenia (HIT);
14. Current or planned use of chronic anticoagulation therapy, including vitamin K antagonists and novel oral anticoagulants (apixaban, rivaroxaban, dabigatran and edoxaban).
15. Peptic ulcer disease with documented active ulcer, or gastrointestinal bleeding within the last year;
16. History of allergy to nickel, or allergy to contrast media that cannot be managed medically;
17. Persistent symptomatic orthostatic hypotension (>20/10 mmHg after 5 minutes of standing upright);
18. Syncope documented to be related to changes in BP within the last six (6) months;
19. History of myocardial infarction, or unstable angina within the past six (6) months;
20. History of cerebral vascular accident within the past year, and NIHSS >5 or mRS >1, or any prior stroke with permanent neurologic defect or any intracranial bleed;
21. Chronic kidney disease (Glomerular filtration rate (GFR) calculated by the Modification of Diet in Renal Disease equation <45 ml/min);
22. Prior carotid surgery, therapeutic radiation, or endovascular stent placement in either carotid region;
23. Severe valvular or structural heart disease (excluding left ventricular hypertrophy);
24. Severe chronic obstructive pulmonary disease, severe asthma or severe pulmonary hypertension (Pulmonary Artery Systolic Pressure PASP>70 mmHg or Pulmonary Vascular Resistance PVR >4.0 Woods Units, not correctable with intravenous diuretics or vasodilator therapy), or any pulmonary disease in which it is expected that the patient cannot lay down without experiencing dyspnea for the duration of the procedure and post-procedural care;
25. NYHA class III or IV heart failure or known reduced left ventricular function (ejection fraction (EF) <30%);
26. Uncontrolled diabetes mellitus with HbA1c >=10 %;
27. Clinical suspicion or history of vasculitis or other condition causing vasculitis (e.g. autoimmune disorders);
28. Active infection within the last month requiring antibiotics;
29. Uncontrolled co-morbid medical condition, including mental health issues, that would adversely affect participation in the trial (including adherence with all follow-up procedures);
30. Co-morbid condition that reduces life expectancy to less than one (1) year;
31. Planned surgery or other procedure within the next six (6) months requiring cessation of

antiplatelet medications;
32. Pregnant or lactating females. For females of child-bearing potential, a positive mandatory pregnancy test within seven (7) days of the pre-randomization screening or refusal to use a medically accepted method of birth control for the duration of the screening period and trial;
33. Presence of visible atherosclerotic plaque or areas of intimal thickness (IMT) of >1500 micron in the region of the carotid bifurcation (15 mm proximal and 15 mm distal to the ICA ostium), determined at a central core laboratory;
34. Significant obstructive vascular disease, calcification or plaque of aortic arch and great vessels by ultrasound, CTA or MRA;
35. Renal artery stenosis >50% or systolic gradient >10 mmHg in borderline cases diagnosed by renal artery imaging in the 36 months prior to signature of informed consent. Acceptable renal artery imaging modalities include renal duplex, MRA, CTA, and selective or non-selective renal angiography depending on trial site diagnostic standards;
36. Internal carotid artery (ICA) lumen diameters <4.5 mm or >12.5 mm within the planned location of the implant placement via CTA or MRA. Evidence of landing zone restrictions, such as inadequate length, vessel tapering, and/or vessel curvature that would preclude safe placement of the implant;
37. Enrolled in a concurrent clinical trial of an investigational drug or device that has not yet reached its primary endpoint or may otherwise interfere in study processes or endpoints;
38. Unable or unwilling to fulfill the protocol follow-up requirements;
39. Subject is a prisoner or member of other vulnerable population. ;Day of Procedure - Angiographic:
1. Evidence of any carotid plaque, ulceration or any stenosis on selective carotid angiography performed in orthogonal views. ICA luminal diameter <5 mm or >11.75 mm within the planned location of the device placement;
2. Any angiographic evidence of plaque or ulceration in the aortic arch and/or the supra-aortic vasculature;
3. Inappropriate anatomy of the carotid bifurcation for deployment of the MobiusHD, including, but not limited to, tortuosity of the extracranial vessels and significant angulation of the common carotid artery bifurcation;
4. Type III arch or horizontal takeoff of the left carotid from the innominate and any significant calcification of the carotid bulb.

Study design

Design

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

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-08-2017
Enrollment:	80
Type:	Actual

Medical products/devices used

Generic name:	MobiusHD device
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	10-11-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	06-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
ClinicalTrials.gov	NCT02804087
CCMO	NL57167.100.16