CALM-2 - Controlling and Lowering Blood Pressure with the MobiusHD*

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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	Not approved
Status	Will not start
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON46497

Source
ToetsingOnline

Brief title
CALM-2

Condition

- Vascular hypertensive disorders

Synonym
drug resistant high blood pressure, resistant Hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Vascular Dynamics
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 from baseline to 180 days post-randomization, between the treatment arm and the sham arm.

Secondary outcome

Exploratory efficacy endpoints are differences in a) in mean day-time and night-time 24-hr ambulatory systolic blood (24hr sABP) from baseline to the 365-day visit. b) in number and dosage of antihypertensive medications from baseline to 90, 180 and 365 days; c) in quality of life scores; d) in healthcare utilization including number of hospitalizations and office visits due to hypertension; between the treatment and sham arms.

Safety will be evaluated by assessing the following:

• Adverse events (AEs)

• Serious adverse events (SAEs)

• Composite measure of death, MI, stroke, device embolization, carotid occlusion, new ipsilateral carotid stenosis requiring surgical or percutaneous intervention, or Bleeding Academic Research Consortium (BARC) 3 to 5 bleeding at the 90-day visit window.

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. "

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, where baseline ambulatory blood pressure, antihypertensive medication compliance and other markers will be measured. 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 follow-up visits. Unblinding of the subjects will occurr at the 1 year F/Up visit (or thereafter) once the last enrolled subject completed the 180 day F/Up visit Subjects who were randomized in the sham arm may decide at that time whether to undergo deferred treatment, or remain in the no treatment group.

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 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

Public
Vascular Dynamics

Kranestraat 67
Horst 5961GX
NL
Scientific
Vascular Dynamics

Kranestraat 67
Horst 5961GX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age 18 to 80
2. Mean Direct Observed Therapy (DOT) 24 hour ambulatory systolic blood pressure >=145 mmHg and <=200 mmHg and stable for at least 8 weeks on a maximally tolerated guideline directed Guideline directed *A+C+D* antihypertensive medication regimen, where *A* is an angiotensin-converting enzyme Inhibitor or an angiotensin receptor blocker, *C* is a calcium channel blocker, and *D* is a diuretic. Patients that have documented intolerance to one or more of these drugs and are on an alternative 3-5 drug regimen will be reviewed and approved by the Hypertension Committee prior to inclusion in the trial.
3. Antihypertensive medication compliance based on DOT-ABPM and HPLC/GCMS analysis of a urine sample
4. Two consecutive DOT 24-hour systolic DOT-ABPM measurements within 20% of each other
5. Adequacy of the carotid anatomy for treatment with the MobiusHD implant based on carotid angiography.

Exclusion criteria

1. Known or clinically suspected baroreflex failure or autonomic neuropathy
2. History of hypertensive crisis in the past 6 months
3. Known significant aortoiliac or common femoral artery disease that will prohibit safe femoral access;
4. 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)
5. Currently taking centrally acting agonists such as clonidine, moxonidine, or methyl dopa;
6. 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
7. Upper arm circumference >46 cm and/or BMI >=45 kg/m2
8. Chronic atrial fibrillation, or intermittent atrial fibrillation with one or more episode(s) within the last twelve (12) months
9. History of major bleeding complications associated with dual anti-platelet therapy
10. History of known uncorrected or uncorrectable bleeding diathesis
11. History of Heparin Induced Thrombocytopenia (HIT)
12. Current or planned use of chronic anticoagulation therapy including vitamin K antagonists and novel oral anticoagulants (apixaban, rivaroxaban, dabigatran and edoxaban)
13. Active gastritis or peptic ulcer disease with documented active ulcer or gastrointestinal bleeding within the last 3 months

14. History of allergy to nickel, or allergy to contrast media or study medications that cannot be managed medically
15. Persistent symptomatic orthostatic hypotension (>20/10 mmHg after 5 minutes of standing upright)
16. Syncope documented to be related to changes in blood pressure within the last six (6) months
17. History of myocardial infarction or unstable angina within the past six (6) months
18. History of cerebral vascular accident (stroke or TIA) within the past year or NIHSS >=5 or mRS >1 or any prior stroke with permanent neurologic defect or any prior intracranial bleed
19. Prior carotid surgery or stent placement, therapeutic radiation to the neck, or endovascular stent placement in either carotid region
20. Severe valvular or structural heart disease (excluding left ventricular hypertrophy)
21. Severe chronic obstructive pulmonary disease (requiring twenty-four-hour oxygen or chronic oral steroids), severe asthma, or severe pulmonary hypertension (Pulmonary Artery Systoic Pressure PASP>70 mmHg or Pulmonary Vascular Resistance PVR >4.0 Woods Units, not correctable with IV diuretics or vasodilator therapy)
22. NYHA class III or IV heart failure or known reduced left ventricular function (EF <30%)
23. Uncontrolled diabetes mellitus with HbA1c >=10 %
24. Clinical suspicion or history of vasculitis or other condition causing vasculitis (e.g. autoimmune disorders)
25. Active infection within the last month requiring antibiotics
26. Uncontrolled co-morbid medical condition, including mental health issues, that would adversely affect participation in the trial (including adherence with all follow-up procedures)
27. Co-morbid condition that reduces life expectancy to less than one (1) year
28. Planned surgery or other procedure within the next six (6) months requiring cessation of antiplatelet medications
29. Pregnant or lactating females. For females of child-bearing potential, a positive mandatory pregnancy test during screening or refusal to use a medically accepted method of birth control for the duration of the trial
30. Carotid duplex studies demonstrating obstructive carotid disease, plaque, ulceration or >150 micron intima-media thickness (IMT) at the site of implantation and/or proximal to the carotid artery bulb and >=50% disease distal to the carotid artery bulb, including the intracranial circulation
31. Chronic kidney disease (eGFR calculated by the Modification of Diet in Renal Disease equation <45 ml/min)
32. Any significant obstructive vascular disease, calcification or plaque of aortic arch and great vessels by MRA
33. Renal artery stenosis >50% or systolic gradient >10mmHg in borderline cases diagnosed by renal artery imaging in the last 12 months performed with acceptable renal artery imaging modalities including renal duplex, magnetic resonance angiography, CT angiography, and selective or nonselective renal angiography depending on trial site diagnostic standards
34. Internal carotid artery (ICA) lumen diameters <4.5 mm or >12.5 mm within the planned location of the implant placement via MRA or evidence of landing zone restrictions, such as inadequate length, vessel tapering, and/or vessel curvature that would preclude safe placement of the implant
35. 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
36. Unable or unwilling to fulfill the protocol follow-up requirements
37. Evidence of any carotid plaque, ulceration or any stenosis on selective carotid angiography performed. Luminal diameters will be assessed to exclude subjects with ICA lumen diameters <5 mm or >11.75 mm within the planned location of the implant. Evidence of landing zone restrictions, such as inadequate length, vessel tapering, and/or vessel curvature that would preclude safe placement of the implant;
38. Any angiographic evidence of plaque or ulceration in the aortic arch and/or the supra aortic vasculature;
39. 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;
40. Type III arch or anatomy that creates for difficult ICA access and any significant calcification of the carotid bulb.
41. If renal angiography is performed due to inadequate renal screening imaging, a renal artery with stenosis of >50% or systolic gradient >10mmHg.
Day of Procedure
1. Evidence of any carotid plaque, ulceration or any stenosis on selective carotid angiography performed. Luminal diameters will be assessed to exclude subjects with ICA lumen diameters <5 mm or >11.75 mm within the planned location of the implant. Evidence of landing zone restrictions, such as inadequate length, vessel tapering, and/or vessel curvature that would preclude safe placement of the implant;
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 anatomy that creates for difficult ICA access and any significant calcification of the carotid bulb.
5. If renal angiography is performed due to inadequate renal screening imaging, a renal artery with stenosis of >50% or systolic gradient >10mmHg.

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:	Will not start
Enrollment:	33
Type:	Actual

Medical products/devices used

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

Ethics review

Not approved

Date:	28-05-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	03-07-2019
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	NCT03179800
CCMO	NL64592.100.18