BradycArdia paCemaKer with AV interval modulation for Blood prEssure treAtmenT (BACKBEAT Trial)

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The primary objective of the study is to determine whether AVIM therapy in combination with medical therapy is more effective at reducing ambulatory systolic blood pressure (aSBP) and to determine whether AVIM therapy is safe.

Ethical review	Approved WMO
Status	Pending
Health condition type	Vascular hypertensive disorders
Study type	Interventional research previously applied in human subjects

Summary

ID

NL-OMON57245

Source
ToetsingOnline

Brief title
BACKBEAT Trial

Condition

- Vascular hypertensive disorders

Synonym
high blood pressure hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Orchestra Biomed, Inc.
Source(s) of monetary or material Support: Orchestra Biomed, Inc.

Intervention

- Medical device

Keyword: Atrioventricular interval modulation, Dual-chamber pacemaker, Hypertension

Explanation

N.a.

Outcome measures

Primary outcome

The primary efficacy endpoint of the study is the between-group difference in
the change of mean 24-hour ambulatory systolic blood pressure (aSBP) reduction
from baseline to 3 months post-randomization.

The primary safety endpoint is freedom from Unanticipated Serious Adverse
Device Effects (USADE) in the treatment group at 3 months.
Note: In the context of safety endpoint evaluations, *Device* refers to AVIM
therapy. All protocol defined safety events will be adjudicated by an
independent Clinical Events Committee (CEC).

Secondary outcome

1) To determine whether AVIM therapy in combination with medical therapy is
more effective at reducing oSBP than medical therapy alone.
Endpoint: The between-group difference in the mean change in oSBP from baseline
to 3 months post-randomization.
2) To determine whether AVIM therapy is immediately effective at reducing aSBP,
minimizing potential impact of adherence to medication on changes in blood
pressure.
Endpoint: The between-group difference in the change of 24-hour aSBP with the
measurement initiated immediately after randomization (mean change within the
first day of activation).
3) To determine the long-term safety of AVIM therapy
Endpoint: Freedom from the composite cardiovascular adverse event (CCAE) rate
at 12 months post-randomization in the Treatment Group will be compared with
that of the Control Group.
4) To determine whether AVIM therapy in combination with medical therapy is
more effective at reducing ambulatory pulse pressure (aPP) than medical therapy
alone.
Endpoint: Between group difference of mean change in 24-hour aPP from baseline
to 3 months post-randomization.
5) To determine whether AVIM therapy has an impact on a hierarchical composite
endpoint that gives appropriate priority to the more clinically important

events while also accounting for the impact of medication usage
Endpoint: A win-ratio analysis will be conducted using a sequence of
comparisons as follows:
- >5 mmHg reduction in aSBP at 3 months;
- >5 mmHg reduction in aSBP at day 1 post randomization; and
- Reduction in anti-hypertensive medication burden as calculated by the defined
daily dose (DDD)(multiply medication dose with the conversion factor for each
medication) at 3 months
A comparison of each pair of patients will be carried out to determine a win,
loss or tie relationship between pairs if the result of the previous comparison
was a tie.
6) To determine whether AVIM therapy in combination with medical therapy is
more effective at achieving a significant reduction in aSBP than medical
therapy alone.
Endpoint: Between group comparison of the percentage of subjects with >=5 mmHg
reduction in 24-hour aSBP (responders) at 3 months post-randomization.</p>

Study description

Background summary

High blood pressure (hypertension) is worldwide one of the the main factors contributing to cardiovascular diseases and mortality. Cardiovascular risk doubles for every 20 mmHg increase in systolic blood pressure. The long-term benefits of reduction in office systolic blood pressure (oSBP) have been demonstrated in large clinical studies. An analysis of 100 studies evaluating approximately 600,000 patients demonstrated that a 10mmHg reduction in oSBP is associated with a risk reduction of major cardiovascular events by 20%, coronary heart disease by 17%, stroke by
27%, heart failure by 28% and all-cause mortality by 13%.
Although there are numerous medications used for controlling blood pressure, many patients continue to have persistently high blood pressure despite their adherence to medical therapies. Investigators have recently turned to alternate strategies to treat hypertension* in particular, device-based therapies.
Hypertension is the most common condition in the pacemaker patient population affecting over 70% of these patients. AVIM therapy is a novel pacing algorithm that when incorporated into a standard dual-chamber cardiac pacemaker system which enables the existing device to treat hypertension while simultaneously delivering standard pacing therapy. AVIM therapy is indicated for the reduction of blood pressure in patients indicated for a dual-chamber pacemaker who also have uncontrolled hypertension (HTN)
despite the use of anti-hypertensive medications.
Results of the clinical studies performed to date provide evidence of the safety and efficacy of AVIM therapy and justifies the conduct of this study to

demonstrate safety, effectiveness, and clinical utility (value of a medical test or treatment in improving patient outcomes) of AVIM therapy. AVIM therapy is being integrated into the Astra/Azure dual-chamber pacemaker system from Medtronic, Inc., which is already approved for clinical use by regulatory bodies worldwide. Rigorous testing has been completed to ensure the compatibility of AVIM therapy with existing features provided by the Astra/Azure device. The Astra/Azure pacemaker system incorporating AVIM therapy will be referred to as the Astra/Azure DR MRI IPG with AVIM therapy.

Study objective

The primary objective of the study is to determine whether AVIM therapy in combination with medical therapy is more effective at reducing ambulatory systolic blood pressure (aSBP) and to determine whether AVIM therapy is safe.

Study design

This is a prospective, multinational, randomized, double-blind, clinical trial evaluating the safety and effectiveness of a novel AV interval modulation (AVIM) algorithm downloaded into a de novo dual-chamber Medtronic pacemaker. The study will be conducted in three phases: 1) Screening/Eligibility, 2) Double-blind Randomized (1 year) and 3) Unblinded (2 years). Patients who are scheduled to undergo implantation of a, or already have an implanted, de novo Astra/Azure pacemaker system, who also have uncontrolled hypertension may be screened for inclusion into this study.
Subjects meeting all eligibility criteria will be scheduled and tested during the Eligibility Phase; subjects will be assessed for eligibility to be randomized at the end of the Eligibility Assessment Phase.
Subjects not meeting eligibility criteria for randomization at the end of the Eligibility Assessment Phase will be exited from the study.
Subjects meeting randomization eligibility criteria will have the investigational AVIM Therapy RAMware downloaded into the Astra/Azure implantable pulse generator (IPG). Once downloaded, AVIM therapy is activated and programmed to settings that achieve a reduction in office systolic blood pressure (oSBP) of at least 5 mmHg (see further details described in Section 12.17 AVIM Therapy Parameter Setting of the protocol). Eligible subjects will then enter the double-blind randomized phase and will be randomized 1:1 to either an active treatment or control group. Subjects in the Treatment Group will have AVIM therapy turned ON and continue to receive antihypertensive drug therapy. Subjects in the Control Group will have AVIM therapy turned OFF and continue to receive antihypertensive drug therapy and standard pacemaker therapy. Subjects will be followed in the Double-blind Randomized Phase for 12-months and will continue to be followed in an unblinded phase for an additional 2 years. At the end of the Double-blind Randomized phase, all subjects will be unblinded and given the option to either remain in the randomized group assigned or crossover.

All subjects will have the investigational AVIM Therapy RAMware removed from the pacemaker and exited from the study after the 3-year follow-up is completed.

Intervention

The novel AV interval modulation (AVIM) algorithm will be downloaded into a dual-chamber Medtronic pacemaker.
AVIM Therapy programming can be set to: AVIM OFF or AVIM ON allowing programming of different parameters related to delivery of AVIM Therapy. AVIM OFF will result in the pacemaker operating as a standard Azure/Astra DR MRI IPG.

Study burden and risks

The AVIM therapy has undergone rigorous bench testing and preliminary pre-clinical and clinical studies to evaluate its safety and performance. Based on the results from preclinical studies and in human studies with hypertension demonstrating a reduction in blood pressure and based on the risk analysis for Medtronic Azure/Astra DR MRI IPG with AVIM Therapy, the potential benefits in treating patients with uncontrolled hypertension outweigh the potential risks. The implant of the Medtronic Azure/Astra DR MRI IPG and pacing leads will occur as per standard of care. The risks associated with the Medtronic Azure/Astra DR MRI IPG and pacing leads can be found in the device labelling and User manuals for the approved devices. After downloading the investigational AVIM therapy, the Medtronic Azure/Astra DR MRI IPG becomes the investigational device for the study.
Potential risks associated with the AVIM program are: Too fast of a heart rate, too slow of a heart rate, development of unusual sensations, feelings or having a fast beating, fluttering or pounding heart, pain or discomfort, symptoms of low blood pressure or high blood pressure (including light headedness, dizziness, loss of consciousness, headache, blurred vision, fatigue or decreased exercise capacity), development of heart failure and/or a reduction in left ventricular ejection fraction or shortness of breath on exertion.
Additional risks and burdens specific to the study include data breach due to a breach in confidentially. However, this will be minimised by carrying out comprehensive training with the Investigator and study team on data protection. For the purposes of this study, no subject identifiable data will be collected. All subjects will be allocated a subject ID number following enrolment into the study and this number will be used for all study related documentation. The information collected will only be used for the purposes of this study. The blood testing required for this study come with discomfort as with any blood draw and include but are not limited to fainting/light-headedness, hematoma/bruising, infection, or the requirement of multiple needle punctures to locate an adequate vein.
In view of the participants clinical condition the risk is not significant, and

the clinical benefit outweighs the long-term risk. The impact of AVIM therapy of the pacemaker battery life will have no impact on the battery longevity beyond that for any patient requiring 100% AV pacing.
There may be more time required from participants during the study visits than would otherwise not be required if they were not participating in the study. Participants may need to visit the site more frequently and for longer periods of time and undergo additional blood tests and blood pressure measurements.
All participants will be monitored throughout the study for the detection of adverse events. All patients will be informed of the potential risks through a detailed patient information sheet and informed consent form. Participants will be encouraged to report anything which is troubling them. There may also be other unforeseeable risks, if any new information becomes during the study, which could influence participant decision to be included, they will be informed.
To control or mitigate the risks associated with study participants, qualified experienced doctors will participants as Investigators along with experienced research staff to perform study assessments. All those involved in the study will receive training prior to working on the study. CVs and qualifications will be checked to ensure those involved in the study are suitably trained and qualified to perform their delegated responsibilities in the study. All Investigators and study personnel will be trained on the AVIM Therapy RAMware-modified dual chamber IPG and its application. All blood pressure measurements and other tests required by the study will be performed in a consistent manner with sound research design. Furthermore, AVIM therapy can be turned off and the AVIM Therapy RAMware can be permanently removed from the device if required at any point during conduct of the study.

Contacts

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Trial sites

Trial sites in the Netherlands

Amsterdam UMC
Target size: 15

MUMC Maastricht
Target size: 15

Listed location countries

Belgium, Netherlands, Poland, Spain, United States, Hungary, Italy, United Kingdom, Switzerland, Germany, Czech Republic

Eligibility criteria

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

Inclusion criteria

- Patient has or is indicated for a de novo dual-chamber pacemaker. The patient informed consent must be obtained within 30 days prior to a planned de novo implant of a Medtronic Astra/Azure dual chamber pacemaker system or up to 365 days after.
- Visit 2 testing and assessments may be initiated only after the subject is on a stable treatment regimen with 1, 2 or 3 classes of antihypertensive drugs (regardless of the reason for which they were prescribed), that is expected to remain stable for a period of at least 3 months post-randomization.
- Office SBP >=140 mmHg and <180 mmHg

Exclusion criteria

- Currently in persistent or permanent atrial fibrillation, which will prevent or limit delivery of AVIM therapy
- Left ventricular ejection (LVEF) fraction <50% (per site assessment)
- Aortic stenosis with a valve area less than 1.5 cm2 (per site assessment)

Study design

Design

Study phase:	N/A
Study type:	Interventional research previously applied in human subjects
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	No intervention
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2024
Enrollment:	30
Duration:	37 months (per patient)
Type:	Anticipated

WORLD

Recruitment status:	Pending
Start date (anticipated):	01-11-2023
Enrollment:	500
Type:	Anticipated

Medical products/devices used

Product type:	Medical device
Generic name:	Astra/Azure DR MRI IPG met AVIM Therapie
Registration:	No

IPD sharing statement

Plan to share IPD: Undecided

Plan description
N.a.

Ethics review

Approved WMO Date:	17-01-2025
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2025
Application type:	Amendment
Review commission:	METC Amsterdam

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	NCT06059638
CCMO	NL86871.000.24
Research portal	NL-005753