Flow Regulation by Opening the SepTum in Patients with Heart Failure; a prospective, randomized, sham-controlled, double-blind, global multicenter study.

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON55919

Source
ToetsingOnline

Brief title
FROST-HF

Condition

- Heart failures

Synonym
Heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Occlutech US LLC
Source(s) of monetary or material Support: industrie

Intervention

Keyword: flowregulator, Heart failure, sham procedure

Outcome measures

Primary outcome

The Primary Efficacy Endpoint is a composite with the following hierarchical testing:

• Incidence of and time to Cardiovascular Mortality through 12-24-months

• Incidence of and time to heart transplant or left ventricular assist device through 12-24-months

• Total rate (first plus recurrent) per patient year of heart failure hospitalization admissions and time-to-first heart failure hospitalization through 12-24-months

• Total rate (first plus recurrent) per patient year of heart failure treatment intensification event and time-to-first heart failure treatment intensification event through 12-24 months

• Change in baseline KCCQ total summary score at 6-months.

The final primary endpoint analysis will occur when the last randomized subject reaches their 12-month follow-up. Data from subjects that have completed any follow-up visits up to and including the 24-month follow-up will be included in the primary endpoint analysis

Secondary outcome

•Clinical Performance, including change from baseline in:

o New York Heart Association (NYHA) Class

o Kansas City Cardiomyopathy Questionnaire (KCCQ)

o Euro Quality of Life 5 Dimension (EQ-5D)

o Change in 6-Minute Walk Test (6MWT)

• Components of primary efficacy endpoint

o Cardiovascular mortality

o Heart failure hospitalization rate

o Heart failure treatment intensification rate

o Heart transplant or LVAD placement

• Device Performance:

o Device placed in-situ as assessed by investigator

o Patency: Evidence of left to right shunt through AFR device as assessed by

core lab

o Implant embolization and clinically significant device migration (i.e.

Serious Adverse Events (SAE)s probably related to device)

Study description

Background summary

The purpose of this clinical study is to assess the safety and effectiveness of the Atrial Flow Regulator in the treatment of subjects, 18 years of age or older, who have symptomatic heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF) while on stable guideline directed medical therapy (GDMT) as outlined in the Guidelines for the Management of Heart Failure. This to reduce Heart Failure outcomes including cardiovascular mortality, transplant or left ventricular assist device implant, heart failure hospitalizations, and to improve quality of life. There are

currently no FDA approved devices for heart failure and the safety of the Atrial Flow Regulator has been demonstrated in a pilot study, therefore, a large randomized study for the Atrial Flow Regulator is the next appropriate study. There is strong evidence to support efficacy for interatrial shunts in heart failure patients.

Study objective

The objective of this study is to investigate whether an interatrial shunt device is superior to sham procedure in prevention of: (1) incidence of and time to cardiovascular mortality through 12-24 months; (2) incidence of and time to heart transplant or left ventricular assist device (LVAD) through 12-24 months (3) first occurrence and recurrence of heart failure hospitalization and time to first heart failure hospitalization through 12-24 months, (4) first occurrence and recurrence of heart failure treatment intensification event and time to first heart failure treatment intensification event through 12-24 months and (5) improvement of Kansas City Cardiomyopathy Questionnaire (KCCQ) total summary score at 6 months.

Study design

The FROST-HF Study is a randomized, double-blind, prospective, multi-center global study comparing the clinical outcomes of the Atrial Flow Regulator to sham procedure. Randomization will be 1:1:1 and will occur immediately prior to procedure.
Up to 150 centers in the U.S., Canada, Europe and Asia Pacific (APAC) may participate in this study.
Approximately 588 subjects will be randomized and an estimated 110 roll-in subjects will be included in the study. A minimum of 50% of the total subjects will come from U.S. sites.
Subjects will be followed for up to 24 months for endpoint analysis and up to 60 months for long term follow-up.
The total duration of the study is expected to be about 7 years - 2 years for enrollment and 5 years follow-up.

Intervention

N/A

Study burden and risks

Risks associated with the device have been estimated in accordance with ISO 14971: Risk Management for Medical Device, prior to conducting the FROST-HF Study. The risk analysis includes an objective review of published and available unpublished medical and scientific data. The residual risks, as identified in the risk analysis, risks to the subject associated with the

clinical procedure against the anticipated benefits to the subjects have been identified.
This risk analysis has been used in identifying anticipated adverse device effects characterized by their nature, incidence, severity, and outcome.
Anticipated Adverse Events, whether device or procedure related, that may be anticipated in subjects undergoing interatrial shunt implant with the Atrial Flow Regulator, another interatrial shunt, or in subjects being treated with study-specified medications (i.e., antiplatelets) are listed in Table 4 of the protocol..

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

Subjects must meet all inclusion criteria: 1) Written informed consent 2) Aged

>=18 years 3) Presence of chronic symptomatic HF (NYHA >=class 2) and at least one of the following: a. Prior heart failure hospitalization within 6 months of informed consent, or b. Increased NT-proBNP within 2 months of informed consent according to the following: i. If LVEF <=40%, then NT-proBNP >1200 pg/mL (or BNP >400) ii. If LVEF >40% with Atrial Fibrillation, then NT-proBNP >900 pg/mL (or BNP >300) iii. If LVEF >40% without Atrial Fibrillation, then NT-proBNP >300 pg/mL (or BNP >100) 4) If LVEF documented at screening is >55%, then must have one of either: a. Left atrial enlargement (LA diameter >2.3 cm/m2 or LA volume index >28 mL/m2), or b. PCWP >= 15mmHg at rest within previous 12 months, or c. LVEDP >=15mmHg at rest within previous 12 months 5) 6MWT distance 100-450 meters 6) Treated with maximally tolerated doses of class I GDMT and class I electrical therapies (CRT and ICD) according to latest applicable guidelines (e.g., AHA or ESC) for at least 2 months prior to informed consent, and a stable (no more than 100% increase or 50% decrease) dose diuretic for at least 1 month prior to informed consent. Note: lack of insurance coverage or affordability is a valid reason not to be treated with a class I agent or device. An attempt to reach maximum dose of GDMT that is not tolerated and followed by successful resumption of the lower stable dose that had been maintained for at least 2 months without clinical instability requires a 1-month waiting period.

Exclusion criteria

Subjects are not eligible for clinical study participation if they meet any of the following exclusion criteria: General Exclusion Criteria 1) Myocardial infarction and/or revascularization with percutaneous intervention (PCI) or coronary artery bypass grafting (CABG) within 3 months prior to informed consent 2) Surgical or transcatheter valve (aortic, mitral, or tricuspid) repair or replacement within 2 months prior to informed consent 3) Automated implantable cardioverter defibrillator (AICD) placement within 2 months prior to informed consent 4) Resynchronization therapy started within 3 months 5) Major surgery within 3 months prior to informed consent 6) History of stroke, transient ischemic attack (TIA), deep vein thrombosis (DVT), or pulmonary emboli within 6 months, or any prior stroke with persistent neurologic deficit, or any prior intracranial bleed, or known intracerebral aneurysm, AV malformation or other intracranial pathology increasing the risk of bleeding 7) Uncontrolled atrial fibrillation with resting heart rate >110 beats per minute despite medical therapy 8) Advanced heart failure defined as ACC/AHA Stage D heart failure 9) Current or recent Heart Failure hospitalization within 4 weeks 10) Documented history of non-dilated cardiomyopathy (obstructive hypertrophic, restrictive, infiltrative) or pericardial disease 11) Clinically significant valvular heart disease: a. regurgitation grade >=3+ or b. severe stenosis of mitral or tricuspid valves, or c. moderate or greater stenosis of aortic valves 12) Prior diagnosis of pulmonary hypertension with current treatment with one or more pulmonary hypertension specific drugs (e.g.

endothelin receptor antagonists (ERAs), phosphodiesterase inhibitors (PDE 5 Inhibitors) or prostacyclin analogues) 13) Uncontrolled hypertension, Systolic Blood Pressure (SBP) >=160 or Diastolic Blood Pressure (DBP) >=100 mmHg despite medical therapy at the time of screening visit 14) Previous interventional or surgical atrial septal defect (ASD) or patent foramen ovale (PFO) closure 15) Inadequate vascular access for implantation of shunt, e.g., suboptimal femoral venous access for transseptal catheterization or inferior vena cava (IVC) is not patent 16) Sepsis or other infection(s) requiring systemic antibiotics 17) Chronic kidney disease currently requiring dialysis 18) Allergy or contraindication to aspirin, or clopidogrel and prasugrel and ticagrelor, or heparin and bivalirudin 19) Bleeding disorders (international normalized ratio [INR] >2.0, platelet count <100,000 x 109/L, hemoglobin <10.0 g/dL) 20) Inability to stop oral anticoagulation 4 days before and 4 days after procedure 21) Known clinically significant untreated carotid artery stenosis likely to require intervention, at discretion of investigator 22) Current untreated coronary artery disease with indication for revascularization 23) Contraindication to transesophageal echocardiography (TEE) or intra-cardiac echo (ICE) 24) Right ventricular systolic pressure >= 70 mmHg on Screening TTE 25) Significant Right Ventricular dysfunction demonstrated by: a. Tricuspid Annular Plane Systolic Excursion (TAPSE) <16mm or b. Right Ventricular Fractional Area Change (RVFAC) <=30% 26) Right Atrial Volume Index (RAVI) > 31 mL/m2 27) Left Ventricular End-Diastolic Diameter (LVEDD) > 8.0 cm as assessed by echocardiography 28) Class 3 or greater angina pectoris 29) Severe COPD requiring oral steroid therapy or daytime oxygen 30) Echocardiographic evidence of intra-cardiac mass, thrombus, or vegetation 31) Congenital heart defect that interferes with placement of the device, at the discretion of the investigator 32) On current immunosuppression or systemic oral steroid treatment 33) Any condition that limits exercise tolerance other than heart failure (e.g., peripheral vascular disease, orthopedic issues, angina, other), at the discretion of the Investigator 34) Participating in another investigational clinical trial that could interfere with this study, at the discretion of the investigator 35) Vulnerable populations including individuals with mental disability, persons in nursing homes, impoverished persons, homeless persons, nomads, refugees and those permanently incapable of giving informed consent; vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces and persons kept in detention. 36) Pregnant or breast-feeding or any intended pregnancy within 12 months after implant 37) Not using an acceptable method of contraception for the first 12 months 38) Any medical non-cardiac conditions with life expectancy less than 1-year 39) Other clinically significant co-morbidities that make the patient unsuitable for study participation, at the discretion of the investigator Intraprocedural Exclusion Criteria: 40) Previous ASD or PFO interventional or surgical closure, current atrial septal defect, or anatomical anomaly (including > 10 mm atrial septal thickness or atrial septal aneurysm) on TEE or ICE that precludes implantation of the device across the fossa ovalis (FO) of the interatrial septum 41) Right Atrial Pressure (RAP)

>12 mmHg on invasive hemodynamics 42) On a right heart catheterization, that should be done within 30 days of implantation, but no later than intraprocedurally prior to randomization: a. Pulmonary Artery Systolic Pressure (PASP) >= 70 mmHg regardless of Pulmonary Vascular Resistance (PVR) or b. PASP >= 50 up to < 70 mmHg with PVR >= 3 Wood Units, unless the PVR can be reduced to less than 3 Wood Units by vasodilator therapy

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Generic name:	Atrial Flow Regulator
Registration:	No

Ethics review

Approved WMO

Date:	27-07-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NCT05136820
CCMO	NL81851.000.22