Prospective, non-randomized, pilot study to assess safety and efficacy of a novel Atrial Flow Regulator in patients with Pulmonary Hypertension

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The primary objective of the study is to evaluate the safety and tolerability of the Occlutech® AFR device by assessing the incidence of SADEs in the 3 months following implantation. Secondary objectives are related to safety and efficacy:• To...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON49991

Source
ToetsingOnline

Brief title
AFR-PROPHET trial

Condition

- Pulmonary vascular disorders

Synonym
high blood pressure in the lungs, Pulmonary hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Occlutech International AB

Source(s) of monetary or material Support: Occlutech International AB

Intervention

Keyword: Atrial Flow Regulator, NYHA class >= III, Pulmonary hypertension, Right heart failure

Outcome measures

Primary outcome

The primary safety endpoint of the study will be assessed after 3 months

following implantation and is defined as the rate of serious adverse device

effects (SADE).

Secondary outcome

Secondary study parameters/outcome of the study (if applicable) (in English):

The following secondary safety variables will be collected within the period of

12 months after implantation and used to assess the safety of the Occlutech®

AFR device:

• Rate of all SAEs;

• Rate of all (S)ADEs

The following secondary efficacy variables will be assessed by comparison of

the values with baseline data and expressed as absolute and percentage changes:

Mechanical Performance

Assessments by color-doppler echocardiography and angiography/fluoroscopy:

• Device placed in situ [as assessed by the Investigator];

• Evidence of RIGHT TO LEFT shunt through the AFR device [as assessed by the

Investigator];

Clinical Performance;

• NYHA status [Classification by investigator];

• Transcutaneous oxygen saturation [%];

• Rate of syncopal events;

• Dosage of diuretics;

• Dosage of PH-related medication.

Functional Variables (ECHO, 6MWT, CPX)

• Ratio of right ventricle size to left ventricle size [mm/mm];

• Size of left ventricle in diastole (cm2);

• 6-Minutes-Walk Test [m];

• VO2max [ml O2/min];

• Transcutaneous saturation at max.

Laboratory Variables

• NT-Pro-BNP [pg/ml];

• Creatinine [µmol/l];

• CholinEsterase [kU/l].

Hemodynamic Variables

• Right atrial pressure (mmHg);

• Right atrial pressure -to Left atrial pressure gradient;

• Cardiac index [(l/min)/m²]

Study description

Background summary

Patients with severe pulmonary hypertension (PH) develop a reduction and decay of the pulmonary vasculature. The right side of the heart should pump the full cardiac output through this narrowed vascular system, which also has high blood pressure and increased pulmonary vascular resistance. In a compensated state, the heart can increase the workload. However, in the course of time the heart can decompensate. This leads to increased pressure in the right atrium. Because the size of the right half of the heart increases, tricuspid dysfunction and eventually heart failure develop in many cases, combined with reduced cardiac output and reduced filling and output of the left side of the heart. Most patients die due to a combination of right heart failure, with low cardiac output from the left.
Patients with PH suffer from reduced exercise capacity and may eventually develop signs of reduced cardiac output and low blood pressure due to right heart failure. Periods of acute increase in pulmonary vascular pressure with acute decrease in cardiac output may lead to fainting. Eventually, these patients die of blocked or significantly reduced blood flow through the pulmonary vascular system and / or arrhythmias due to insufficient coronary perfusion.
By means of an atrial flow regulator (AFR) an artificial connection is established via the interstitutional septum through which blood flows when the volume of blood on the right side is too high. This would reduce the pressure in the right heart side and reduce the clinically important right heart congestion. Furthermore, the left side of the heart gets extra blood volume, which increases stroke volume, cardiac output, blood pressure and organ perfusion. Probably acute fainting and acute right heart decompensation and mortality occurs less.
The usual treatment for patients with severe pulmonary hypertension, which has since been very well described in internationally accepted and published guidelines, is treatment with a variety of medications, including anticoagulants, diuretics, digitalis preparations, oxygen, vasodilators, calcium antagonists, prostacyclines and prostacyclin- analogs, endothelin receptor antagonists and phosphodiesterase inhibitors. Nonetheless, these seriously ill patients usually have a poor prognosis resulting in right heart failure and death. If patients reach NYHA stage III or higher, lung transplantation is the only option for these patients. Currently, patients are often offered balloon atrial septostomy (BAS).
The advantage of BAS is the increase in cardiac output as a result of the extra blood volume by making a passage between the right and left atrium. This relieves the right ventricle and the entire venous system, with reduction of clinical symptoms. The overall survival of patients who have undergone such treatment is increasing. That is why this procedure is used to 'bridge' the

time until actual lung transplantation takes place.
The disadvantage of a BAS is that the artificial passage may be too large, causing dangerous desaturation and potential death. The passage can also be closed by heart cells in the short term, requiring a new intervention, with additional risk burden for the patient.
The AFR is intended to realize both a correct diameter of the artificial passage and to prevent its growth. Atrial flow regulators are considered suitable for treatment of a certain group of patients with pulmonary hypertension according to the most recent international guidelines of the American Heart Association.

Study objective

The primary objective of the study is to evaluate the safety and tolerability of the Occlutech® AFR device by assessing the incidence of SADEs in the 3 months following implantation.

Secondary objectives are related to safety and efficacy:
• To evaluate the safety and tolerability of the Occlutech® AFR device by assessing the incidence of SADEs between 3-12 months following implantation.
• To evaluate the improvement in Right-Heart-Failure in the 3 months, in the 6 months and in the 12 months following implantation;
• To evaluate the improvement in number of syncopal events due to pulmonary hypertension in the 3 months, the 6 months and the 12 months following implantation.

Study design

This is a prospective, non-randomized, pilot study to assess safety and efficacy of a novel Atrial Flow Regulator (AFR) in patients with pulmonary hypertension in a phase-2 design.
Patients will be screened within the week before the implantation of the AFR. Eligible patients who signed the informed consent form will undergo Balloon Atrial Septostomy followed by implantation of the AFR device under standard clinical procedures. Follow up period after implantation will consist of 6 visits in a period of 360 days.

Intervention

Patients will undergo Balloon Atrial Septostomy followed by implantation of the AFR device under standard clinical procedures.

At day of implantation, there will be a catheterization, providing the definition of the PH and for the AFR implantation procedure. Catheterization will be repeated after 3 months to evaluate changed hemodynamics, including fluoroscopy to judge position of the device. This 3 months FU is in common

practice in the EU and USA and is, together with the radiation burden within the currently accepted mode of care.
Catheterization will be conducted according to a study specific catheterization protocol.

During the course of the study, blood is collected for laboratory analysis, ECGs and transthoracic echocardiography are made and 6-miutes walking test and Cardiorespiratory Test with lung function are conducted.

Study burden and risks

Patients with PH are often offered BAS. The advantage of the BAS is the gain in cardiac output due to the additional blood volume provided by the right-to-left shunt through the BAS. This, on the other side of the heart, offloads the right ventricle and the entire venous system, with reduction of the clinical symptoms. Survival of such treated patients is increased, thus, this procedure is used to *bridge* the time until actual lung transplantation is happening.

Potential risks related to the intended use and foreseeable misuse of the Occlutech® AFR are identified and mitigated on an ongoing basis. Anticipated potential risks of the Occlutech® AFR device are associated with:
• Device contamination
• Vessel or unintended and excessive cardiac perforation
• Use of oversize or undersize device
• Complications of transseptal puncture
• Wrong size dilatation balloon selection
• Wrong usage of delivery system
• Device design is not suitable for the septal puncture morphology
• Use of wrong/incompatible sheath (system)
• Use of incompatible pusher: Pusher size is larger or smaller than it is supposed to be
• Incorrect positioning of device

Risk control measures were undertaken to reduce the probability of unacceptable and borderline acceptable risks. Where ever possible, priority was given to mitigating the risk first through design changes to eliminate it and if this was not feasible, by integrating protective measures in the medical device itself or in the manufacturing process to minimize the risk. Risks due to human factors that could not be eliminated or checked in advance, such as mistakes in the implant or explant procedures will be mitigated by including clear warnings and cautions in the literature and packaging accompanying the device and by limiting implantation use to experienced and trained interventional cardiologists.

As described in section 5.3, a full risk analysis was performed during the development of the Occlutech® AFR device to anticipate and eliminate or at least minimize all foreseeable

Occlutech® AFR device related risks. However - as with any new device - it is possible that unknown risks remain that will only become apparent as more experience is gained with the device. The safety of the study patients is of paramount importance and will be monitored throughout the study at all times.

It is possible that the study will show the Occlutech® AFR device is not suitable for its intended use. In this event, future patients will be spared exposure to the Occlutech® AFR device and information may have been gained to develop alternatives. Patients in this study may still have benefitted from their participation in the form of a closer follow-up and a positive altruistic feeling.
Patients will be requested to attend visits on a regular basis. It is possible that this will be uncomfortable or inconvenient for them. Patients will be reminded that the information they provide is confidential, that it will be used to better the care they and fellow patients receive, and that their continued participation is voluntary.

The disadvantage of an atrial septostomy is
• artificial shunt may be too large
• may occlude within the short term
• may result in repeat BAS
• anticoagulation with Warfarin and analogues is recommended life-long
Advantage of the AFR device is:
• securing the BAS to remain open
• preventing BAS oversizing and systemic desaturation
• plasmatic anticoagulation is not necessary, platelet inhibition should occur for 6 months
• the ability to plan the size of the intended right-to-left shunt creates further safety in this specific intervention and in the care of the patient in general
• the expected absence of above complication in these severely ill and unstable patient will likely result in less morbitiy and mortality.

In conclusion, the benefits of AFR devices outweigh by far the procedural and device related risks.

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

Each patient must fulfill ALL of the following criteria and details:1. Age is >= 18 / >= 6 years (Phase 1 / Phase 2).
2. Patient consents to participation
3. The patient or his/her legal representative should have the ability to fluently speak and understand
the language in which the study is being conducted. If the patient speaks a different language,
then a sentence-to-sentence translation for unequivocal understanding must be provided.
4. Written, informed consent by the patient or her/his legally-authorized representative for participation in the study.
5. Patient agrees to comply with the follow-up schedule.
6. Patient has had a successful BAS procedure and is in a stable hemodynamic state, as assessed by the Investigator
7. Conventional treatment options for the patient are exhausted according to European Society of Cardiology and American Heart Association guidelines
8. SpO2 >= 86 % (pulsoxymetric measurement)Further, the patient must fulfill ALL criteria and details of
EITHER *Syncope* (Group-A-PH) OR *RV-Failure* (Group B-PH).9. *Syncope* (Group-A-PH)
9.1. Syncope due to acute PH episodes (as defined by exclusion of other causes)

9.2. Other causes of syncope must have been actively excluded
9.3. Syncope (Black-out) or pre-syncope (episodic dizziness) >2 last 3 months
9.4. PH (defined as mean pulmonary artery pressure > 25 mmHg, or pulmonary vascular resistance
of > 3 Wood Units) must exist, RV-failure is however not a prerequisite.10. *RV-Failure* (Group B-PH)
10.1. Right heart failure, chronic and clinically severe
10.1.1. NYHA class III or worse
10.1.2. 6 min walk < 320 m
10.1.3. Signs of venous congestion (distended veins, edema, ascites, etc)
10.1.4. Symptomatic disease resulting in 1 or more PH-related hospitalization over the last 12
months. Elective hospital admissions solely for the purpose of performing diagnostic procedures
do not count for this.10.2. Severe pulmonary hypertension as evident by echocardiography
Echocardiographic:
10.2.1. RV larger than LV;
10.2.2. RA larger than LA;
10.2.3. Atrial septum bulging into left atrium
10.2.4. Ventricular septum bulging into the left ventricle
10.2.5. Reduced (below age-related normal mean value) TAPSE10.3. Severe pulmonary hypertension as evident by CATH
CATH-data:
10.3.1. Mean RA pressure (RAP) >= 10 mmHg and <= 20 mmHg;
10.3.2. Mean LA pressure (LAP) <= 15 mmHg
10.3.3. Mean RAP > mean LAP;
10.3.4. Mean pulmonary arterial pressure >25 mm Hg
10.3.5. Echocardiographically demonstrated continuous right to left shunt following balloon
atrial septostomy (BAS) and before AFR device implantation
sible risks of c

Exclusion criteria

A patient must be denied access to the study if one or more of all the following criteria are present as evaluated by medical history, laboratory test or other, as appropriate:Processes which interfere medically with invasive device implantation
1. Local or generalized sepsis or other acute infection(s)
2. Thrombophilic coagulation disorder
3. Allergy to nickel and/or titanium and/or nickel/titanium-based materials
4. Allergy to anti-platelet, -coagulant, or -thrombotic therapy
5. Intolerance to contrast agents
6. Participation in other medical trials shorter than 30 days before the

intended AFR implantation
procedure
7. Pregnancy - (assessed in patients with child bearing potential by urine dip stick)
8. Any intracardiac intervention within the last 30 days
9. Thickness of atrial septum > 12mmORProcesses which would technically disturb the safe intervention as planned
1. Occluded inferior vena cava access
2. Previous ASD/PFO closure device in place
3. Intracardiac thrombusORany other circumstance that, in the opinion of the Investigator, might interfere with the implantation, might affect the patient*s well-being thereafter or might interfere with the conduct and follow-up within the study in general.
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Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	6
Type:	Actual

Medical products/devices used

Generic name:	Atrial Flow Regulator
Registration:	No

Ethics review

Approved WMO

Date:	08-08-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-05-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-12-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NCT03022851
CCMO	NL67794.042.19

Study results

Date completed:	11-05-2022

Summary results

Trial never started