A randomized, controlled study to evaluate the safety and cardiovascular effects of Algisyl-LVR* as a method of left ventricular augmentation in patients with dilated cardiomyopathy (AUGMENT-HF)

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The objective of the AUGMENT-HF study is to provide evidence for the safety profile associated with the Algisyl-LVR* device and initial evidence for the efficacy of the device.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON38421

Source
ToetsingOnline

Brief title
AUGMENT-HF

Condition

- Heart failures

Synonym
heart failure, reduced pump function of the heart.

Research involving
Human

Sponsors and support

Primary sponsor: LoneStar Inc
Source(s) of monetary or material Support: LONESTAR HEART;INC.

Intervention

Keyword: Chronic heart failure, Dilated cardiomyopathy, Medical device

Outcome measures

Primary outcome

1. The primary safety outcome is to estimate the 30 day mortality associated with the implantation of the Algisyl-LVR device;

2. The primary efficacy outcome is the change in Peak VO2 from baseline to 6 months of follow-up.

Secondary outcome

1. Incidence of major surgical complications (30 days post op);

2. Incidence of major anesthesia-related complications;

3. Incidence of major adverse cardiac event (MACE). MACE is defined as cardiac death, cardiac arrest, myocardial infarction, sustained ventricular arrhythmias, pulmonary edema, acute heart failure, unstable angina and major bleeding (6 months);

4. Overall incidence and freedom from serious adverse events (6 months);

5. All-cause mortality and cardiovascular mortality (6 months);

6. All-cause hospitalizations and heart failure hospitalizations (6 months);

7. Time to first heart failure hospitalization (6 months);

8. Number of days alive out of hospital (all cause) during the 1st 6 months;

9. Laboratory assessments (6 months);

10. Adverse events;

11. Cardiac imaging (Echo and MRI or Nuclear Imaging) measures of changes in

left ventricular volume, ejection fraction, dimensions, and mitral

regurgitation (6 months);

12. Six-minute walk distance (6 months);

13. Quality of life as measured by KCCQ (6 months);

14. Patient Global Assessment (PGA) (6 months);

15. NYHA Functional Class (6 months).

Study description

Background summary

Heart Failure (HF) results in poor life expectancy, impaired quality of life, repeated hospitalisations and is a considerable economic burden, accounting for 1-2% of health care expenditure in European countries. The incidence of HF approaches 10 per 1000 population after 65 years of age, and approximately 80% of patients hospitalised with HF are older than 65 years. Despite current drug and device therapies for the treatment of HF, its prognosis remains poor. In addition, the treatment choices for patients with advanced HF are limited and include for the most part heart transplantation, left ventricular assist devices, or biventricular pacing. However, these therapeutic solutions are not an option for all HF patients because of either clinical contraindications or economical considerations.
Structural abnormalities in the heart are known to play a central role in HF, and clinical evidence supports a strong causal relationship between cardiac chamber dilatation and HF. Because dilation, and not contractile dysfunction, appears to be responsible for the severity of the disease, the mitigation or prevention of the deleterious dilation process appears to be an important therapeutic target for patients with this diagnosis. Hence, a therapy that specifically targets progressive Left Ventricular (LV) dilatation and remodeling by thickening the LV wall, reducing wall stress and reducing the LV chamber size may offer an important new alternative in the treatment of HF.
The medical device under investigation in this study is called Algisyl-LVR*. This is a novel medical device and procedure intended to prevent or reverse the progression of LV remodeling in dilated cardiomyopathy. Alginate is a polysaccharide hydrocolloid found as a structural component in marine brown

algae. The product is highly biocompatible (cytotoxicity, mutagenicity, hemolysis, irritation or sensitization) and the kinetics of the alginate have been tuned such that Algisyl-LVR is similar in functional properties to myocardial tissue; a spongy, compliant material. Two different alginate components form a calcium cross-linked hydrogel minutes after mixing, thus is readily injectable. Alginate polymers do not biochemically degrade in higher organism tissues.
The tissue engineering principles employed with Algisyl-LVR target the most critically important aspect of the failing ventricle by directly reducing wall stress (improving myocyte performance) and strategic, targeted reduction of the inner chamber radius. This approach is unique and avoids the potentially unintended negative consequences of other therapies such as altering diastolic performance, peripheral hemodynamics or increasing myocyte workload.

Algisyl-LVR is implanted (injected) directly into the myocardial tissue during a single surgical (cardio-thoracic) procedure. The implants are intended to be permanent and serve to increase LV wall thickness, reduce LV wall stress and result in a reduced LV chamber size with an improved pumping efficiency. The placements of the implants also serve as a prosthetic scaffold that prevents ongoing ventricular enlargement and restore a more beneficial shape to a dilated left ventricle. Experimental data demonstrates that the device produces an immediate and sustained improvement in cardiac function.
The intended clinical benefits of Algisyl-LVR are to improve the failing heart*s structure and function with an associated improvement in the patient*s clinical status and quality of life.
For further information, see study protocol (version 1.1. dated June 20th 2011) page 13, introduction and page 19, study rationale.

Study objective

The objective of the AUGMENT-HF study is to provide evidence for the safety profile associated with the Algisyl-LVR* device and initial evidence for the efficacy of the device.

Study design

AUGMENT-HF is a prospective, controlled, randomized, multi-centre trial with two parallel groups of equal size. Eligible patients will be randomized (randomization will be concealed) to either the Investigational Device Group or to the Usual Care group. The moment of randomization will be the starting point of follow-up and the starting point of follow-up for surgical mortality and surgical complications will be as of the date when the cardio-thoracic procedure is performed (or attempted). The primary safety outcome is 30 day all-cause mortality associated with the implantation of the Algisyl-LVR device. The primary efficacy outcome is change in Peak VO2 from baseline to 6 months of follow-up. The secondary outcomes will evaluate the effects of the device,

relative to the control group through functional, structural, biochemical and electrocardiographic evaluations performed at 3, 6 and 12 months following randomization. Patient safety will be overseen by an Independent Data Safety Monitoring Board. Study outcomes will be adjudicated by a Clinical Endpoint Committee (CEC) blinded to study group allocation. The cardiopulmonary exercise data, cardiac imaging, blood tests and 24-hr Holter Monitor data will be evaluated by central core laboratories, all blinded to study group allocation.
Patients assigned to the Aligysl-LVR group will have the Algisyl-LVR* device (implant) administered during a surgical procedure which will be scheduled between 7 to 10 days after randomization.
Patients randomly assigned to control group will be treated for their heart failure in accordance with the current recommendations. After having completed the 12-month follow-up visits, patients assigned to the control group will be provided the option of enrolling in Clinical Study LSH-11-001: An Open Label Rollover Trial for Patients Randomized to the Control Group of Study LSH-10-001. Patients must meet the inclusion and exclusion criteria as stated in Study LSH-10-001 to be eligible for Study LSH-11-001 and to receive the Algisyl-LVR* device.
The follow-up in this study is divided into two phases - the *efficacy* phase and *extended follow-up phase*. The efficacy phase will end after the last randomized patient has completed the 6 month visit. During this time, all patients will be contacted by telephone 30 days after randomization and will be seen at the out-patient clinic at 3 and 6 months after randomization to undergo repeat testing of functional and cardiac structural parameters in addition to a Quality of Life Assessment. The primary efficacy and secondary safety and efficacy outcomes will be analyzed at this time-point. During the *extended follow-up* phase, patients will return to the out-patient clinic every 6 months until each patient has completed, in total, 24 months of follow-up. During this phase, data collection will be focused on long-term safety.

Intervention

Patients randomized to the Investigational Device group will be admitted to the hospital within 7 and 10 days after randomization to undergo the cardio-thoracic surgical procedure employing a limited anterolateral thoracotomy (approximately 10 to 15 cm) to implant Algisyl-LVR. It is expected that the surgery will last maximally 1 hour. To ensure patient safety, standard intraoperative monitoring tools will be utilized which will include continuous cardiac monitoring, arterial pressure lines, transesophageal echocardiography, and pulmonary artery pressure measurements. The surgeon will administer the Algisyl-LVR device as described in the Algisyl-LVR Instructions for Use Manual. The Cardiac surgeons will undergo adequate, documented training prior to implanting the device. In addition, the surgeon will be proctored by a cardiac surgeon who has previously implanted the Algisyl-LVR device. It is expected that patients will remain in hospital up to maximally 8 days following the procedure.

Study burden and risks

1. Burden and risks:
The nature and extent of the risks and benefits associated with participation in the AUGMENT-HF study is detailed in section 14 of the trial protocol (version 1.1, dated June 20th 2011). In addition, all identified known risks are described in the Algisyl-LVR Investigator Brochure (version 5.1, dated August 09th 2011).

Risks associated with the cardio-thoracic surgery:
Patient risks or discomforts may be expected to include any of the standard risks of a patient undergoing cardiothoracic surgery.

Risks associated with the investigational device:
Possible risks due to the investigational device may include arrhythmias from heart manipulation during device placement. Thrombo-emboli resulting from either dislodgment of any intracardiac thrombus or inadvertent penetration of the device (hydrogel) into the LV cavity during device placement could result in stroke, pulmonary embolism, myocardial infarction, or peripheral embolism. Like all implanted devices, this investigational device may increase the risk of infection. Hemodynamic compromise could result from an improper use of the device, from damage to coronary arteries or abrasion of the heart surface during device placement. However, animal studies have evaluated the effects on cardiac tissue and have found no evidence of problems when the device is implanted. Animal testing has also demonstrated that the device implant is biocompatible.

Evaluation of the occurrence of events such as excessive fibrosis or constrictive disease related to the investigational device will be monitored throughout the duration of the study. No such events have been observed to date in either animal or human studies. If the physician determines that cardiac compression or damage related to device placement, subsequent fibrosis formation, or tissue response is resulting in hemodynamic compromise not treatable by cardiac medication alone, the following surgical options are available:
• Superficial grid-like scoring of the epicardial surface to release constriction. The medical literature contains reports of several successful applications of this technique in patients with constrictive pericarditis associated with constrictive epicarditis. See: Heimbecker R, et al., Surgical Technique for the Management of Constrictive Epicarditis Complicating Constrictive Pericarditis (The Waffle Procedure), Annals of Thoracic Surgery, Vol 36, No 3, Nov 1983. See also: Faggian G, et al., Constrictive Epicarditis After Open Heart Surgery: The Turtle Cage Operation, Journal of Cardiac Surgery, Vol 5, No 4, 1990;
• Placement of cardiac assist or replacement device (unless the patient has contraindications);

• Cardiac transplant (unless the patient is contraindicated for transplant).

The risks for participation in this study have been minimized by:
• Selection of experienced clinical sites;
• Adequate and documented training of the cardio-thoracic surgeon. In addition, the surgeons will be proctored for the first two patient cases;
• Adequate training of the other members of the site team that will be responsible for the follow-up of the patients during the study.
• A rigorous patient selection (i.e. strict inclusion and exclusion criteria defined in the study protocol);
• A Data Safety Monitoring Board (DSMB) will be responsible to oversee patient safety. The committee will review the patient data at pre-specified time points during the conduct of the study;
• Clear and unambiguous stopping rules have been defined in the study protocol (see section 4.1, page 21 of the study protocol, version 1.1, dated June 20th 2011). The DSMB will be responsible to implement the stopping rules;
• Frequent monitoring: Frequent on-site monitoring visits will be performed to ensure proper conduct and management of the study.

2. Potential Benefits
The benefits to patients participating in this study will include the recognition that they are contributing to a better understanding of the potential use of the Algisyl-LVR device. Patients may benefit from closer monitoring of their health. Patients allocated to the Algisyl-LVR group may show improvement in clinical signs and symptoms related to their cardiac disease in addition to an improvement in Health-Related Quality of Life.

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

1. The patients must be able and willing to give written informed consent;
2. The patients will be adult (age >= 18 years and <= 79 years) males or females;
3. The patients must be on stable, evidence-based therapy for heart failure;
4. The patients will have a left ventricular ejection fraction equal to or less than 35% via echocardiography, cardiac catheterization, radionuclide scan, or magnetic resonance imaging (measured within the last 30 days);
5. The patients will have a left ventricular end diastolic dimension indexed to body surface area (LVEDDi) of 30 to 40mm/m2 (LVEDD/BSA) (measured within the last 30 days);
6. Patients must have symptomatic heart failure with a Peak VO2 of 9.0 - 14.5 ml/min/kg (performed using a bicycle ergometer). Patients must perform two CPX tests (within 30 days of randomization and performed at least 20 hours apart) that differ by no more than 15% in the observed value for Peak VO2 and have a mean value of 9.0 - 14.5 ml/min/kg from these two tests;
7. Patient*s surgical risk must be considered reasonable and the evaluation of surgical risk should include review of coronary and left ventricular angiography;
8. If female, the patients must be (a) post-menopausal, (b) surgically sterile, or (c) using adequate birth control and have a negative serum pregnancy test within 7 days prior to administration of study device.

Exclusion criteria

1. Patients for whom it is planned to receive CABG, MVR, heart transplantation or LVAD within the next 6 months;
2. Patients presenting with cardiogenic shock;
3. Patients who have undergone a previous mid-sternotomy surgical procedure are excluded unless the surgeon*s assessment is that the left sided limited thoracotomy is feasible and considered reasonable surgical risk;

4. Patients presenting with a restrictive cardiomyopathy such as due to amyloidosis, sarcoidosis, or hemochromatosis;
5. Patient with a history of constrictive pericarditis;
6. Patients with a Q wave myocardial infarction (MI) within the last 30 days;
7. Patients with a recent history of stroke (within 60 days prior to the surgical procedure);
8. A left ventricular (LV) wall thickness of the LV free-wall, at the midventricular level, of less than 8 mm (screening echocardiography must confirm a minimum wall thickness of 8 mm);
9. Patients with a serum creatinine > 2.5 mg/dL;
10. Clinically significant liver enzyme abnormalities, i.e., AST(SGOT) and ALT (SGPT) more than 2.5 times the upper limit of normal;
11. History of severe COPD (i.e., FEV 1< 1 liter or FEV1 < 50% predicted);
12. The patients will not be receiving concurrently an investigational Product in another clinical trial or have received an investigational Product in another clinical trial in the 30 days prior to enrollment;
13. A life expectancy of less than 1 year or any other condition that, in the opinion of the clinical investigator, might compromise any aspect of the trial.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-11-2012
Enrollment:	18
Type:	Actual

Medical products/devices used

Generic name:	Algisyl-LVR

Registration:	No

Ethics review

Approved WMO Date:	05-07-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-08-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-09-2013
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
CCMO	NL37005.100.12