INcrease Of VAgal TonE in chronic Heart Failure (INOVATE-HF) - A randomized study to establish the safety and efficacy of Cardiofit for the treatment of subjects with heart failure and left ventricular dysfunction.
A pivotal trial to establish the long-term safety and efficacy of the cardiofit system.

Published: 03-08-2011
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To determine the efficacy and safety of the CardioFit system for the treatment of subjects with systolic heart failure who have failed to achieve symptom relief through standard evidence-based management per applicable guidelines.

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

Summary

ID

NL-OMON41238

Source
ToetsingOnline

Brief title
CardioFit Pivotal Study for the treatment of Heart Failure.
INOVATE-HF

Condition

- Heart failures

Synonym
Heart failure

Research involving
Human

Sponsors and support

Primary sponsor: BioControl Medical (B.C.M.) Ltd.
Source(s) of monetary or material Support: BioControl Medical (B.C.M.) Ltd.

Intervention

Keyword: Cardiofit, Heart-Failure, Vagal stimulation

Outcome measures

Primary outcome

Primary safety endpoints

The co-primary safety endpoint of the study is a composite of the following:

a) Lower 95% confidence interval of freedom from procedure and system related

complication events through 90 days post implant > 70%; and

b) Comparison of time to first event of all-cause mortality or all-cause

complications resulting in hospitalization (including complications

contributing to prolongation of hospitalization, collectively referred to as

safety events) during the up to 5 year follow-up of each study subject

between the two study arms with a log hazard ratio non-inferiority margin

equivalent to 12.5% margin at 1-year.

Primary efficacy endpoint

The primary efficacy end-point of the study is the composite of all-cause mortality or unplanned heart failure hospitalization equivalent using a time to first event analysis, as compared between the two study arms after a pre-specified number of such events have been accumulated.

Secondary outcome

Secondary Endpoints

There are four secondary endpoints which are designed to further demonstrate symptomatic improvement of study participants tested according to the gatekeeping procedure described in the statistical plan. Additional details on the statistical approaches are provided in the Statistical Analysis Plan.

There are 4 secondary efficacy endpoints which will be tested according to the statistical gatekeeping procedure described in the statistical analysis plan.

* The rate of unplanned heart failure hospitalization equivalents
* Mean improvement in LVESVi from baseline to 12-months
* Mean improvement in the summary score of the KCCQ from baseline to 12-months
* Mean improvement in 6 minute walk test from baseline to 12-months

The following secondary safety endpoint data will also be evaluated.

- All-cause mortality
- Cardiovascular mortality
- Serious adverse events
- Complication

- System- or procedure-related complications

Study description

Background summary

The clinical syndrome of congestive heart failure (CHF) is the result of a number of conditions affecting the heart, preventing the heart to properly meet the systemic demands for blood circulation. Common conditions leading to heart failure are: hypertension, ischemic heart disease, valvular disease, familial cardiomyopathy and infectious, toxic, metabolic or idiopathic causes. In some cases these conditions co-exist and accelerate the progression of ventricular dysfunction.
Heart failure is a chronic disease, beginning with early signs of ventricular remodeling and progressing to severe symptoms and functional handicap. When cardiac failure ensues, the affected person experiences a decrease in the ability to carry out activities of daily living characterized by symptoms of fatigue and shortness of breath at increasingly minimal efforts. There is general fluid retention manifested in most subjects by weight gain and edema particularly of the feet and ankles.
The prognosis for subjects with heart failure is poor. Thirty to forty percent of subjects with advanced disease and 5-10% of subjects with mild disease die within five to ten years.
Heart failure has reached the size of a pandemic. It is estimated that over 5.5 million people in the USA alone suffer from the condition, with more than half a million new cases diagnosed each year. Approximately 1.2 to 2% of the general adult population suffer from heart failure, and in the age group over 65 years old, the prevalence is as high as 10%. The cost of hospitalizations for heart failure is twice that for most forms of cancer.
Pharmacologic antagonism of the beta-adrenergic system, potentially shifting autonomic balance by blunting sympathetic drive, is a well-proven treatment for heart failure subjects, although there are subjects who cannot tolerate, or only partially benefit from such a treatment.
Experimentally, direct parasympathetic stimulation (via the vagus nerve) has been shown to induce equivalent biological effects potentially by restoring parasympathetic tone and reducing the workload of the heart. Therefore, the potential benefits of vagus nerve stimulation for the treatment of heart failure may be substantial. It has been shown before that vagus nerve stimulation might reduce the occurrence of sudden death associated with healed myocardial infarction. Recently it was shown that chronic stimulation of the vagus nerve improved survival in a rat model of heart failure. Preliminary preclinical data in the canine HF model (ischemic) demonstrates favorable effects on remodeling.
Implanted neurostimulators, which stimulate the cervical vagus nerve, have been

successfully used in humans for treatment of refractory seizures and depression for more than 10 years. The therapy is safe, well tolerated and associated with few side effects.

Study objective

To determine the efficacy and safety of the CardioFit system for the treatment of subjects with systolic heart failure who have failed to achieve symptom relief through standard evidence-based management per applicable guidelines.

Study design

This study is designed as a prospective, randomized, open label, prospective, event-driven interventional global study.
It is expected that 650 subjects will be recruited to the study overall to provide up to 400 events. The independent Data Safety Monitoring Board (DSMB), Clinical Event Committee (CEC) and the FDA will review safety data for the CardioFit system in an ongoing manner.

Intervention

The implantation of the CardioFit* system (in the implanted arm) is due 7-21 days post-randomization and takes place in three steps as follows, per the device IFU.
a. Implantation of the Intracardiac Sensing Electrode (ISE).
b. Implantation of the CardioFit* Stimulation Lead (CSL).
c. Implantation of the CardioFit* Implantable Stimulator (CIS).
In order to prevent infection, and inflammation the following preventive steps will be taken:
(1) Subject will be provided with antibiotics pre- and post-procedure, according to the clinical site policy on prevention of infective diseases; and
(2) During the procedure, preventive anti-infection measures will be taken such as use of sterile technique and irrigation of the implant sites with antibiotics; and
(3) Subjects who present with signs of infection, such as body temperature above normal (37oC or 98.6o F will not be included in the study until those signs are cleared.

Study burden and risks

The treated group:
Echo grafic controls at baseline and during follow-up
Blood testing at baseline and during follow-up
Questionaires regarding Quality of life
6minute walk testing
X-rays of the chest

Pulmonary function testing
Holter-recording
Implantation of the cardiofit device. This is a risk in this population, but this is described above already.

Controle group:
Normal care, with a little more frequency of controle moments. The questionaire and 6min walking test will be an extra moment/intervention for the patiënts, but we don't think this will be a risk/problem for the patiënts.

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 with LV systolic dysfunction (EF<40%) and heart failure in NYHA functional class III,

who are on, and have failed to achieve symptom relief despite standerd evidence-based management per applicable guidelines.

Exclusion criteria

Presence of a life threatening condition or disease other than heart failure, such as cancer, terminal renal failure or a progressive neurological disorder, that is likely to lead to death within 180 days.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-03-2012
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	CardioFit
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	03-08-2011
Application type:	First submission

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	07-03-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	26-09-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	18-03-2013
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	17-09-2015
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)

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	NCT01303718
CCMO	NL35011.068.11