AUTONOMIC REGULATION THERAPY TO ENHANCE MYOCARDIAL FUNCTION AND REDUCE PROGRESSION OF HEART FAILURE WITH REDUCED EJECTION FRACTION (ANTHEM-HFrEF)

Published: 06-02-2019
Last updated: 12-04-2024

Primary Objective: The primary objective of this randomized controlled study is to assess the safety and efficacy of the VITARIA* System when added to stable, guideline-directed medical therapy for patients with heart failure and reduced left...

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

Summary

ID

NL-OMON48571

Source
ToetsingOnline

Brief title
ANTHEM-HFrEF

Condition

- Heart failures

Synonym
decompensatio cordis, heart failure

Research involving

Human

Sponsors and support

Primary sponsor: LivaNova USA
Source(s) of monetary or material Support: LivaNova (fabrikant).

Intervention

Keyword: ART, autonomic regulation therapy, heart failure, vagus nerve

Outcome measures

Primary outcome

The primary efficacy endpoint will be a composite of cardiovascular mortality or heart failure hospitalization, based on time to first event after randomization, as adjudicated by an independent Clinical Events Committee (CEC). The primary safety endpoint will consist of the event-free rate, through 90 days after VITARIA implantation, from all VITARIA system-related and VITARIA implantation-related serious adverse events.

Secondary outcome

If the primary efficacy and primary safety endpoints achieve statistical significance, treatment groups will be compared on the following key secondary endpoints:

* Mean change in the quality of life (KCCQ) from baseline to 9 months

* Proportion of subjects who have an improvement in NYHA class from baseline to 9 months

* Rate of unplanned HF hospitalization equivalents from baseline

If all 3 key secondary endpoints are met, treatment groups will be compared on

the following endpoint:

- Mean change in LVEF from baseline to 9 months

Treatment groups will also be compared on the following secondary endpoints:

* Mean change in 6-minute walk distance from baseline to 9 months

* Mean change in LVEDD, LVESD, and LVESVi from baseline to 9 months

* Rate of hospitalization-free days from baseline

* Change in NYHA class from baseline to 9 months

* All-cause mortality

Study description

Background summary

Previous pre-clinical and clinical studies have shown that vagus nerve stimulation restores autonomic balance, reduces systemic inflammation, and provides a functional benefit in heart failure. Based on this research, the ANTHEM- HF feasibility study was conducted to test the VITARIA system in 60 patients receiving stable guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (LVEF * 40%). Chronic therapy with the VITARIA system significantly improved ejection fraction, a variety of other measures of cardiac function including 6 minute walk distance, and heart failure symptoms. The positive results of the ANTHEM-HF study need to be confirmed in a larger, controlled clinical study.

Autonomic Regulation Therapy (ART), delivered via vagus nerve stimulation (VNS) using the VITARIA system, significantly improves clinical outcomes in patients who have symptomatic heart failure and a reduced left ventricular ejection fraction while receiving stable
guideline-directed medical therapy.

Study objective

Primary Objective: The primary objective of this randomized controlled study is

to assess the safety and efficacy of the VITARIA* System when added to stable, guideline-directed medical therapy for patients with heart failure and reduced left ventricular ejection fraction. The data from this study may be used to support marketing applications for the VITARIA system in the United States and other International markets.

Study design

Study Design: Multi-center, open-label, randomized, controlled clinical trial with an adaptive design. Patients with symptomatic heart failure and reduced LVEF will be enrolled and randomized 2:1 to receive VITARIA system implantation on the right cervical vagus nerve (therapy) in addition to stable GDMT (therapy arm), or to continue receiving stable GDMT alone (control arm). Randomization will be stratified by region (as determined by the Steering Committee); distance walked in baseline 6-minute walk test (300 m or less, or more than 300 m); type of study site (cardiac transplantation site or not); and by use of Entresto® (sacubitril/valsartan; yes/no), to ensure proper balance of the treatment groups across the study, and will incorporate blocking of sizes 3, 6, or 9 patients within each strata

Subjects in the therapy arm will receive continuous, periodic VNS stimulation after surgery is completed, and will undergo visits for VNS up titration over a period of 3 months. Subjects in the control arm will also undergo scheduled visits at the same frequency as the titration visits that are scheduled for subjects in the therapy arm

Data for safety and efficacy assessments will be collected for both study arms at 4 weeks postrandomization, every 3 months for the first 12 months, and every 4 months thereafter.

Efficacy will be determined by time-to-first-event of cardiovascular mortality or heart failure hospitalization following randomization. Device safety will be determined by the event-free rate from all system and implantation-related serious adverse events during the 90 day period after randomization. An interim assessment of symptomatic improvement will be made and potentially used to support an early regulatory submission.

Intervention

The VITARIA System lead will be implanted on the right cervical vagus nerve. After the lead and IPG are connected, the surgical/cardiovascular team will perform standard diagnostic testing to ensure proper implantation. In the event that right cervical implantation cannot be accomplished, the subject will not be implanted but will continue to be followed, based on the "intention to treat" design of the study. VNS stimulation will be activated after completion

of implantation, before the patient departs from the procedure room. VNS stimulation will be activated using the following stimulation parameters: output current = 0.25 mA; frequency = 5 Hz; pulse width = 130 µs; duty cycle = 14 seconds on, 66 seconds off

Study burden and risks

Visit schedule: patients require a considerable number of titration visits to reach the right treatment level of the device. The protocol leaves room for a maximum of 9 titration visits in a period of 3 months (weekly visits the first 6 weeks, and bi-weekly the next 6 weeks).

Risks:
The most commonly reported side effects of VITARIA are voice alteration, pain, paresthesia, dyspnea, pharyngitis, and increased cough.
Other potential risks are:
Surgery-related; hematoma, infection, pain, voice alteration (hoarseness).
Stimulation-related: dyspepsia (indigestion), dysphagia (difficulty swallowing), dyspnea (difficulty breathing, shortness of breath), increased coughing, laryngismus (throat, larynx spasms), pain, paresthesia (prickling of the skin), pharyngitis (inflammation of the pharynx, throat), satiety (reduced appetite), sensation of stimulation, voice alteration (hoarseness).

Contacts

Public
LivaNova USA

Cyberonics Blvd 100
Houston TX 77058
NL
Scientific
LivaNova USA

Cyberonics Blvd 100
Houston TX 77058
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

4 Currently in sinus rhythm (extrasystoles are allowed; CRT or CRT-D recipients who have been receiving CRT for at least 6 months, and ICD and pacemaker recipients, may enter the study; paroxysmal and persistent atrial fibrillation are allowed if the patient is currently in sinus rhythm5. Guideline Directed Medical Therapy for at least 4 weeks6. Stable symptomatic NYHA III; or II with a HF hospitalization within the previous 12 months7. Left ventricular ejection fraction (LVEF) <=< 35% (verified by central core lab) and left ventricular end-diastolic diameter (LVEDD) <8.0 cm,8. NT-proBNP > 800 pg/mL as determined by the core-laboratory, as long as the patient reports having experienced no signs or symptoms of atrium fibrilation during the 3 days preceding the NT-proBNP measurements . 10. Baseline 6 Minute Walk Test (6MWT) between 150 and 450 meters

Exclusion criteria

1. Refractory symptomatic hypotension (SBP <80 mmHg)2. Pacemaker therapy that utilizes unilateral ventricular pacing with a right ventricular lead for complete AV block
3. Currently implanted with VNS, BAT or VAD4.Persistent atrial fibrillation or ablation of atrial fibrillation in the past 3 months5. Within last 6 weeks:
Pacemaker or ICD implant
CV hospitalization (including TIA and syncope)
Epigastric or upper gastrointestinal bleeding6. Scheduled, or likely to be scheduled within the next 3 months for
a. Cardiac contractility modulation (CCM), CRT, VNS, BAT or other device implantation for improving ventricular function; or non-cardiac organ transplant
b. A therapeutic cardiovascular procedure (including but not limited to PCI, CABG, valve replacement or repair, aorta surgery, or ablation for arrhythmia management7. Heart failure of non-ischemic origin for less than 6 months, or due to congenital heart disease, hypertrophic obstructive cardiomyopathy, or

infiltrative cardiomyopathy (e.g. amyloidosis, sarcoidosis)

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:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Generic name:	VITARIA System;VITARIA Pulse Generator (Model 7103);VITARIA Leads (Model 7304);and VITARIA Programme
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	06-02-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-07-2019

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL66852.041.18