Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients

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The objective of this study is to assess the safety and effectiveness of the WISE System (providing LV pacing) when used in conjunction with a co-implanted system (ICD, pacemaker, CRT-P, or CRT-D) for bi-ventricular (BiV) pacing for CRT in heart...

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

Summary

ID

NL-OMON55596

Source
ToetsingOnline

Brief title
SOLVE CRT

Condition

- Heart failures

Synonym
cardiac failure, heart failure

Research involving
Human

Sponsors and support

Primary sponsor: EBR Systems, Inc.
Source(s) of monetary or material Support: ERB Systems Inc

Intervention

Keyword: Cardiac Resynchronization Therapy, Heart failure, non-responders, WiSE System

Outcome measures

Primary outcome

Primary Safety

Freedom from Type 1 Complications through 6M compared to a performance goal of 70% for all enrolled in Part II Randomized + Part III Single-arm subjects.

Primary Efficacy 1

Mean relative (%) change in LVESV from baseline to 6 months in PU-HRU subjects with WiSE CRT system switched ON after implantation compared to a performance goal of - 9.3 %.

The primary efficacy endpoint analysis will be done in PU-HRU Treatment arm subjects from Part II Randomized and Part III Single-arm subjects.

Secondary outcome

Secondary Efficacy 1

Electrode Acoustic Pacing Capture Threshold (APCT) measured at the 6-month follow-up post-implant visit (in the Treatment arm).

Secondary Efficacy 2

Electrode Acoustic Pacing Capture Threshold Stability (APCT Stability) measured

from predischarge through the 6-month follow-up post-implant visit

Ancillary

LVESV Distribution Shift, defined as the percentage of subjects with an improvement of greater than 15% in LVESV, from baseline through 6 months.

The mean change in NT-proBNP from baseline, compared between arms (baseline to 6 months.)

The mean change in intrinsic QRS duration, compared between arms (baseline to 6 months).

The percent subjects with at least a one class improvement in NYHA. (baseline to 6 months).

Study description

Background summary

Standard application of CRT, or biventricular pacing (BiV), involves the placement of a right ventricular (RV) lead for pacing the right ventricle and a coronary sinus (CS) lead in an epicardial coronary vein to provide LV pacing. CRT is a recognized device therapy for heart failure that has been studied extensively for over 20 years, leading to a large body of knowledge supporting the therapy and elucidating its challenges and limitations. CRT is currently the standard of care in patients who have LV dysfunction, mild to severe heart failure, symptoms despite optimal medical therapy, and QRS prolongation. CRT is currently recommended for use by the ACC/AHA/HRS guidelines (Epstein 2012) for a number of subsets of heart failure patients based on evidence from large scale randomized trials.
Patients who do not respond clinically to CRT (non-responders) have been

reported in the range of ~ 30% (Abraham 2002, McAlister 2007, Foley 2009). A review of observational studies of CRT has shown non-responders ranged from 18 to 45 percent with a variety of definitions of non-response (Foley 2009).

Another group of patients, described here as previously untreatable, exist because of failed LV lead implants or other LV lead issues (high thresholds, phrenic nerve stimulation, and dislodgement) that result in inability to provide CRT therapy. Due to the varied anatomy of the CS vasculature and difficulty with access preventing LV lead placement, some patients are not able to receive CRT. Failed implants due to lead placement in the CS are high, with reported rates in the ~ 5-10% range (Leon 2005). Unsuccessful LV lead placement in the MIRACLE study was shown to be 7.6%, 5% in CARE-HF, and 13% for CRT-P and 9% for CRT-D in COMPANION (Matsumoto 2007). Additionally, a substantial rate of perioperative and postoperative complications also exist (~ 5-10%) (Leon 2005, Linde 2008).

Additionally, there is a group of patients who are considered high-risk upgrades (HRU) in whom standard CRT upgrade is not advisable due to known relative contraindications to CS lead implant.

The WiSE System is designed to provide leadless pacing on the LV endocardium as well as patient specific selection of the LV pacing site location. The system (in conjunction with a co-implanted device, i.e. pacemaker or defibrillator) is comprised of a wireless endocardial LV electrode that is inserted transarterially or transvenously, allowing for placement throughout the LV as compared to the limited choices afforded by the coronary veins. The electrode is powered wirelessly using ultrasound delivered by a subcutaneously implanted transmitter. This approach potentially resolves many of the issues associated with current methods of CRT. It has been designed to provide endocardial pacing without the stroke and TIA risks of placing a standard pacing lead inside the LV. It allows for LV stimulation at a pacing site of choice rather than only locations dictated by the coronary venous anatomy. It avoids using the coronary venous system on the epicardial aspect of the LV for lead implant, thereby potentially eliminating access, placement, perforation, occlusion, infection, phrenic nerve and pacing threshold issues.
EBR Systems seeks to study the safety and effectiveness of the WiSE System as an alternative to current methods of LV pacing in CRT. A large unmet clinical need exists in patients who have not responded to conventional CRT or who are defined as previously untreatable due to LV lead related issues. It is expected that LV endocardial pacing as well as selection of an LV pacing site specific to the patient may improve the outcome in these patients.

Study objective

The objective of this study is to assess the safety and effectiveness of the WISE System (providing LV pacing) when used in conjunction with a co-implanted system (ICD, pacemaker, CRT-P, or CRT-D) for bi-ventricular (BiV) pacing for

CRT in heart failure patients.

Study design

This study is a prospective clinical trial which is comprised of three seperate multi-center, multicountry parts:

Part I Roll-in, single-arm, open label
Part II Randomized, two-arm, randomized 1:1, double blind
Part III Single-arm, singele-arm, open label

Subjects will be considered enrolled after they consent, pass the study inclusion and exclusion criteria and undergo anesthesia/sedation for implant of the WiSE CRT system.

For Part II Randomized subjects only, after successful implant, the WiSE CRT system will be programmed to OFF until randomization. The subjects in the randomization cohort will be assigned to either the Treatment or Control Arms, employing a 1:1 randomization to the Treatment Arm (WiSE ON) and Control Arm (WiSE OFF).
Part I , Roll-in subjects and Part III, Single-arm subjects will be programmed to WiSE ON following the procedure and followed similarly to subjects in the Treatment Arm.

Patients will undergo scheduled evaluations at pre-implant, pre-discharge/randomization, 1 month (window to cover wound check period +/-21 day), 3 months, 6 months and every 6 months post implantation until the 24 month follow-up.Hereafter patients will be checked year 3, year 4 and year 5. Endpoints will be evaluated through 6 months. After their 6 months evaluation patients in the Part II Control Arm will be programmed to WiSE ON.

Intervention

implantation of a WiSE System. The system will be programmed ON in the active group at discharge. The system wll be programmed OFF at discharge in the control group. In the last group the system will be programmed ON at 6 months.

Study burden and risks

As with any medical procedure or implantable device, the study device implantation procedure and the implanted device carry potential risks and potential benefits. In addition to the known potential risks described below, the device may pose additional potential risks, the nature of which are unknown. Participation in this study may benefit enrolled patients by providing CRT to those previously unable to receive a CRT or providing another opportunity to

those who currently are not responding to CRT. The participating patients may receive improved delivery of CRT and the resultant benefits of improved cardiac function. In addition, the clinical data obtained from this study may benefit other patients with CHF requiring CRT in the future.

Risks related to the implantation procedure
Potential risks related to the implantation procedure include but are not limited to:
• Access site and pocket complications (e.g. pain, bruising, bleeding, infection)
• Air embolism (air bubble in your blood stream)
• Air embolism, permanent injury or death due to air embolization and infarction of distal organs
• Allergic reactions to sedatives, drugs, or other materials used during the implant procedure
• Anemia
• Anesthesia related complications
• Aortic valve damage
• Arterial perforation, dissection, spasm
• Cardiac arrhythmias
• Cardiac tamponade
• Chronic nerve damage
• Death
• Device explant
• Dissection of the aorta or branch vessels (including femoral artery)
• Electrochemical burns
• Embolization of device or material, thrombus, or air to systemic circulation increasing stroke and peripheral vascular occlusion risk, possible organ damage, or death
• Esophagaeal bleeding(after TTE)
• Excessive bleeding
• Femoral artery complications
• Fever
• Hematoma at surgical incision, device pocket or arterial insertion site (blood collected outside the vessel)
• Hemolysis
• Hypotension or hypertension (low or high blood pressure)
• Infection and/or sepsis
• Internal myocardial tissue damage, infract, hematoma
• Kidney injury due to imaging contrast use
• Migration of device implanted
• Mitral valve damage
• Myocardial infarction (heart attack)
• Myocardial tissue (heart muscle) injury or perforation
• Overexposure to x-ray fluoroscopic radiation
• Pain
• Pericardial effusion (fluid build-up around heart)

• Pneumothorax (collapsed lung)
• Pulmonary complications including embolism, respiratory failure and pneumonia
• Renal failure, possibly requiring dialysis
• Septal defect (if transseptal access is used for device implnat)
• Shock
• Sore throat (after TEE)
• Small risk of bleeding, heart attack or stroke (if intra-cardiac echocardiography is done)
• Stroke or transient cerebrovascular events
• Thrombus formation/thromboembolism (blood clot)

WiSE System specific:
• Embolization/migration of the electrode or other delivery system material, possible organ damage, death, or prolonged hospitalization*

Risks related to the post implant period
In addition to the known potential risks from the implant procedure, known post implant risks of the WiSE System include many of the same risks associated with the use of any commercially available CRT system as well as those unique to the WiSE System which include but are not limited to:
• Breach of battery or battery connections
• Device migration
• Early battery depletion
• Electronic or mechanical component failure
• Excessive fibrotic growth
• Fluid accumulation in implant pockets
• Foreign body reaction (allergic reaction)
• Fracture or damage to the battery connection cable
• High rate or competitive ventricular pacing
• High rate ventricular pacing or inappropriate timed pacing that could lead to arrhythmia or death
• Inadvertent device reprogramming
• Need for invasive procedure to correct system problem or effect
• No pacing therapy delivery or loss of pacing capture
• Pain
• Psychological disturbances (dependency, depression, fear of battery depletion, fear of malfunction)
• Skin erosion over implanted device (device exposed through skin)
• Worsening heart failure

WiSE System specific
• Embolization/migration of device requiring surgical intervention, possible organ damage, death, or prolonged hospitalization
• Inability to deliver therapy due to insufficient energy delivered to receiver
• Inappropriate synchronization/pacing (oversensing/undersensing), i.e interference from external ultrasound sources
• Mechanical injury causing tissue damage

• Thermal tissue injury from transmitter elements

Potential Risks of the WiSE System
• Some components, e.g., residuals and/or extractables, of the devices may accumulate at the lesion site and/or in downstream tissues and may cause an adverse biological response. Preliminary animal data suggest this is not occurring, but it is unclear whether the animal data will be directly applicable to patients due to differences in metabolism.
• Some components of the devices contain titanium. Patients sensitive to titanium or have a known titanium allergy should not use this device.
Risks related to the study conduct

The risk increase for subject participating in the study might be related to the new technology featured in the device and to procedures required in the study. However it is expected that study participation may also benefit the subjects due to the close scrutiny of their device function and rigorous identification of adverse events.
Repeated follow-ups limit the risk of sub-optimal device setting. The procedures and methods for data collection required by the protocol do not differ significantly from routine CRT implantation and follow-up practice in CRT subjects.
Use of the device not in conformance with this investigational plan and/or with the Instructions for Use could introduce other issues.

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. Patient with a class I or IIa (1) or (2) indication for implantation of a CRT-D device according to current available guidelines (with additional QRS criteria on Class IIa (1) and EF criteria minimum on all classes):
a. Class I: NYHA II, III, IV, EF <= 35%, LBBB, QRS>=150ms
b. Class IIa (1): NYHA II, III, IV, EF<=35%, LBBB, QRS>=130 to <150ms
c. Class IIa (2): NYHA II, III, IV, EF<=35%, non-LBBB, QRS>=150ms
2. Non-responder*: Patients who have a CRT system that is functional and despite an adequate trial of Guideline Directed Medical Therapy (GDMT) and attempts at optimal device programming the patient has not responded to therapy for a minimum of 6 months. Non-response is defined as remailing clinically unchanged or worsened:
a. EF has remained unchanged or worsened (defined as < 5% increase since implant), and
b. The patient*s clinical status based in the totality of available clinical evidence (such as NYHA
Class, exercise tolerance, QOL, or global assessment) has remained unchanged or worsened, as
determined by the local Site Enrollment Committee (Site Enrollment Committee is made up
of at least one electrophysiologist and a designated Heart Failure Specialist (MD).
OR
Previously Untreatable: Patients who have a full or partial CRT system, who meet general inclusion criteria and are deemed as *previously untreatable* for one of the following reasons:
a. Patients in whom CS lead implantation for CRT has failed
b. CS lead implanted but has been programmed OFF
OR
. High risk upgrades:patients with relative contraindications to CS lead implant
3. Patients on a stable GDMT
4. Patient must be 18 years old or over

5. Signed and dated informed consent
6. Patient has suitable anatomy for implant of the WiSE CRT System (e.g. adequate
acoustic window, LV wall thickness in target implant area >= 5 mm, absence of LV wall
structural abnormalities which may preclude implant)

Exclusion criteria

1. Pure RBBB
2. LVEDD >= 8cm
3. Non-ambulatory or unstable NYHA class IV
4. Contraindication to heparin, chronic anticoagulants or antiplatelet agents
5. Triple anticoagulant patients who cannot tolerate peri-procedural stopping of anticoagulation therapy must be excluded
6. Patients with planned or expected lithotripsy treatment post-implant
7. Attempted device implant (pacemaker, ICD, CRT, LV lead) or successful co-implant
within the prior 30 days
8. Life expectancy of < 12 months
9. Chronic hemodialysis
10. Stage 4 or 5 renal dysfunction defined as eGFR < 30
11. Grade 4 mitral valve regurgitation
12. Noncardiac implanted electrical stimulation therapy devices
13. Patients with a prosthetic aortic valve and a non-viable transseptal approach for the electrode implant.
14. Patients with a prosthetic mitral valve and a non-viable transseptal approach for the electrode implant
15. Unstable angina, acute MI, CABG, or PTCA within the past 1 month
16. Correctable valvular disease that is the primary cause of heart failure
17. Recent CVA or TIA (within the previous 3 months)
18. Patients with a history of paroxysmal or persistent atrial fibrilation/flutter are excluded if they have had a documented
AF episode > 30 min or a cardioversion in the past 30 days from screening.
19. Patients with permanent AF are excluded if they have intact AV node conduction (RV pacing >95%)
20. Already included in another clinical study that could confound the results of this study
21. Pregnancy
22. Known drug or alcohol addiction or abuse
23. Moderate or severe aortic stenosis
24. Positive test for COVID-19 at screening
25. Subject unable to attend follow-up at the investigative center or unable, for physical or
mental reasons, or to comply with the trial's procedures

26. For Part II randomized patients, those who will not tolerate being randomized to the Control Group for 6 months

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-07-2018
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	WiSETM - Wireless Stimulation of the Endocardium System (WiSE CRT System is an implantable cardiac s
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	28-11-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	27-09-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-07-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-03-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-07-2024
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	NCT02922036
CCMO	NL62355.075.17