Prospective non-randomised post-market study collecting clinical data on safety and effectiveness of the remed*®-System

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This study aims to assess the safety and efficacy of the remed*® system in adult patients with moderate to severe central sleep apnea in real life.

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

Summary

ID

NL-OMON53885

Source
ToetsingOnline

Brief title
r*ST Study

Condition

- Heart failures
- Sleep disturbances (incl subtypes)

Synonym
respiratory arrest during sleep, sleep apnea

Research involving
Human

Sponsors and support

Primary sponsor: Zoll Respicardia Inc.

Source(s) of monetary or material Support: Industry - Manufacturing Company (Zoll Respicardia Inc)

Intervention

Keyword: Central sleep apnea, Implantable device, Phrenic Nerve Stimulation, Post Market trial

Outcome measures

Primary outcome

Safety endpoint: Proportion of subjects with peri-operative and long-term

serious adverse events (SAEs) related to the remed* System implant procedure,

device or delivered therapy.

Efficacy endpoint: Change from baseline to 12-month visit for the following

sleep metrics measured during in-lab polysomnogram (PSG): apnea hypopnea index

(AHI), central apnea index (CAI), oxygen desaturation index 4% (ODI4), percent

of sleep with oxygen saturation <90%

Secondary outcome

Safety endpoint: Proportion of subjects with non-serious AEs related to the

remed* System implant procedure, device or delivered therapy

Efficacy endpoints:

- Change from baseline to 36- and 60-month visits for the following sleep

metrics during an at home sleep apnea test (HSAT): apnea hypopnea index (AHI),

central apnea index (CAI), oxygen desaturation index 4% (ODI4), percent of

sleep with oxygen saturation <90%

- Epworth Sleepiness Scale (ESS) change from baseline to 12-month visit.

- Quality of life assessment including the following: Kansas City

Cardiomyopathy Questionnaire (KCCQ) change from baseline at 12 months (HF

subgroup only), PROMIS-29 questionnaire change from baseline at 12 months,

Patient Global Assessment (PGA) at 12 months

- Change in left ventricular ejection fraction based on echocardiographic

assessment in the HF subgroup from baseline to 12 months.

Study description

Background summary

Central sleep apnea (CSA) is a sleep disturbance that manifests as periods of shallow or no breathing followed by resumption of breathing, often with periods of rapid, deep breathing.
Central sleep apnea may occur in an idiopathic form, but more often occurs in patients with co-morbidities associated with an increase in sympathetic drive. Most commonly, these conditions are related to cardiovascular diseases such as heart failure and atrial fibrillation, but may be seen in patients with chronic kidney disease, diabetes mellitus and stroke. In contrast to obstructive sleep apnea (OSA), closure of the airway is not causative of the hypopnea or apnea with CSA. Instead, CSA results from a failure of the brain to send appropriate signals to the respiratory muscles to stimulate a breath. In heart failure, the most common cause of CSA, the breathing signal failure is due to a delay in feedback of changes in carbon dioxide (CO2) levels to the respiratory control center in the brain coupled with an increase loop gain in respiratory control. Consequently, the brain does not initiate breathing until the CO2 level has raised significantly above the normal level, and then responds withrapid deep breathing that continues until the CO2 level is far below normal levels which leads to a *pause* of breathing.
The sleep disturbances caused by CSA have devastating effects. Each apnea and hypopnea event experienced with CSA contributes to a progressive cycle of hypoxia, arousals from sleep, and sympathetic activation, all of which have multiple deleterious effects. The
hypoxia and arousals diminish the quality of sleep and are associated with fatigue and decreased mental acuity. The hypoxia caused by CSA leads to myocardial ischemia and poor cerebral perfusion, which has been associated with dementia. Increased sympathetic drive
results in increased blood pressure, fluid retention, myocardial fibrosis, and ventricular and

atrial arrhythmias. These physiologic disturbances related to CSA have been independently associated with morbidity and mortality. Based on the pathophysiological mechanisms summarized above, it is clear that CSA has a detrimental effect, and treatment is
needed to minimize the downstream effects of the disease.

The sponsor of the trial ZOLL Respicardia Inc. developed a treatment option for adult patients, the remed*® system, to treat moderate and severe CSA. The device is an implantable system that stimulates a nerve in the chest cavity (the diaphragmatic nerve) so that it sends signals to the large muscle between your chest cavity and your abdominal cavity (the diaphragm). These signals stimulate breathing just as the brain stimulates breathing.
The remed*® system activates the therapy automatically and throughout the night.

The remed*® system is an implantable nerve stimulator approved and CE-marked by the US Food and Drug Administration (FDA) for the treatment of moderate to severe central sleep apnea in adult patients.

Study objective

This study aims to assess the safety and efficacy of the remed*® system in adult patients with moderate to severe central sleep apnea in real life.

Study design

This is a multi-center, prospective, open label, non-randomized study to collect safety and
effectiveness data in subjects implanted with the remed*®-System. Enrollment will continue
until approximately 500 enrolled subjects are successfully implanted. Approximately 50 sites
in the United States and Europe will participate.

An individual subject*s participation is expected to continue through five years post remed*®-System therapy activation. Subjects will be seen for an in-office visit 45 days post implant for a PSG prior to therapy activation and then to activate therapy activation. At 6, 12, 24, 36, 48 and 60 months post therapy activation, subjects will be seen in-office for assessments such as sleep studies, questionnaire completion, and other assessments. Subjects who have been clinically diagnosed with heart failure (HF) that has been documented in their medical records (signs or symptoms or prior heart failure hospitalization or BNP >=150 pg/mL or NT-proBNP >= 600 pg/mL) will follow the same visit schedule, but undergo additional HF specific assessments. All subjects will be contacted by phone at 18, 30, 42 and 54 months post remed*®-System activation to assess patient status and adverse events.

All study sites in The Netherlands will participate in a sub-study involving the WatchPAT home sleep apnea testing (HSAT) device.
WatchPAT is a simple home sleep apnea device that utilizes a wrist-worn unit, finger probe, and chest sensor to identify respiratory events and determine which events are centrally mediated based on Peripheral Arterial Tonometry (PAT) signal and other physiologic signals. WatchPAT is an FDA-cleared home sleep apnea test (HSAT) approved for the identification of central sleep apnea and is well established for use in home sleep testing.The purpose of the WatchPAT sub-study is to compare in-lab attended polysomnogram (PSG) data with simultaneous WatchPAT data in patients with historical evidence of central sleep apnea and implanted with the remed*®-system.
The WatchPAT device will be placed on the non-dominant hand during the Therapy Activation visit (prior to activation) and 12-month (active therapy) PSG completed as part of the r*ST study.

Study burden and risks

The potential risks of participating in this study are listed below. Patients participating in this study are subject to similar risks as all patients receiving the remed*® system but not participating in this study.

- There is a risk that the needle prick of blood collection may hurt. There is a small risk of bruising and fainting as a result of the blood draw, and in rare cases there is a risk of infection.
- There is a risk of skin irritation due to the adhesive tape and electrode contact with your skin during your polysomnogram and echocardiogram taken at the sleep centre.
- In rare cases, there is a risk that pressure from the echocardiography probe may cause minor bruising.
- There is a risk that your heart failure symptoms may be worsened by the 6-minute walk test
worsened. If you are concerned about anything during the test, alert the person taking the test immediately.
- There are no additional risks associated with the study for you if you let your study doctor collect data about you and the remed*® system.

Benefit:
New Therapy of Central Sleep Apnea where the patient can have a benefit and availability of the therapy (no reimbursement in the Netherlands) can be a difference for patient and additional co-morbidities that are associated with the disease can be avoided.

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

-Moderate to severe central sleep apnea (AHI >= 15 events per hour) based on a sleep study scored by a local sleep laboratory. It is strongly recommended that a patient have a diagnostic PSG within 12 months of the expected implant date documenting moderate to severe CSA.
-Age 18 years or older
-Signed approved informed consent
-In the opinion of the investigator, subject is willing and able to comply with the protocol.
-Not currently enrolled in another investigational study or registry that would directly interfere with the current study, except if the subject is participating in a mandatory government registry, or a purely observational registry with no associated treatments. Each instance should be brought to the attention of the sponsor to determine eligibility.
-In the opinion of the Investigator, life expectancy exceeds one year.

-The subject is not pregnant or planning to become pregnant.

Exclusion criteria

The subject is pregnant or planning to become pregnant

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-07-2019
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	remed System
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	27-02-2023
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	06-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	NCT03884660
CCMO	NL83217.028.22