Long Term Observational Study Of The Safety And Efficacy Of An Active Implantable Vagal Nerve Stimulation Device In Patients With Rheumatoid Arthritis

Published: 16-02-2012
Last updated: 01-05-2024

Primary Efficacy ObjectiveThe primary efficacy objective is to determine the long term efficacy of vagal nerve stimulation as assessed by the DAS28 score.Secondary Efficacy ObjectivesThe secondary efficacy objectives are to determine the long term...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON43838

Source
ToetsingOnline

Brief title
SPM-006

Condition

- Autoimmune disorders

Synonym
painful swollen joints

Research involving
Human

Sponsors and support

Primary sponsor: SetPoint Medical Corporation
Source(s) of monetary or material Support: Industry - Setpoint Medical Corp.

Intervention

Keyword: Arthritis, Device, Nerve, Stimulation

Outcome measures

Primary outcome

Primary Endpoint

• Change in DAS 28 score from the baseline of the preceding study (SPM-005) to each follow-up visit

Secondary outcome

Secondary Endpoints

• The ACR 20, ACR 50, and ACR 70 response rates calculated based on RA assessments at the baseline of the preceding study compared to those at each follow-up visit on the current study

• The EULAR response rate calculated based on RA assessments at the baseline of the preceding study compared to those at each follow-up visit on the current study

• Change in Euro-QoL score from the baseline of the preceding study to each follow-up visit

Safety Endpoints

The following Safety Endpoints will be assessed:

• Adverse Events

• Serious Adverse Events

• Device Deficiencies

Study description

Background summary

Rheumatoid Arthritis (RA) is a devastating disease which affects approximately 1% of the population causing pain, and limiting physical activity and employment. RA leads to permanent physical deformity and disability from incompletely controlled inflammation and resultant structural damage to the joints. In the last decade, the emergence of antagonists of tumor necrosis factor (TNF)-alpha and other biological response modifiers as treatments for RA has greatly improved the course and prognosis. Despite these advances, there remains a great medical need as current treatments have significant safety and cost disadvantages (McInnes, 2010).
The Cholinergic Anti-inflammatory Pathway (CAP) is an important physiological regulator of inflammation. A wealth of preclinical evidence suggests that activation of this pathway through electrical stimulation of the vagus nerve (VNS) can also be a feasible and effective means of reducing pathological systemic inflammation, and thus may represent a novel approach to treating RA and other human inflammatory diseases (Tracey, 2009; van Maanen, 2009a).
This hypothesis was tested in a pilot study (SPM-005) in which RA patients were surgically implanted with a commercially available vagal nerve stimulation device and the clinical safety and efficacy of neurostimulation of the cholinergic anti-inflammatory pathway (NCAP) was assessed using standard clinical measures and surrogate biomarkers of RA.
The aim of the current protocol is to determine the long term safety and efficacy of NCAP in the patients who previously enrolled in study SPM-005.
The SPM-006 substudy has the aim to investigate the effect of vagal nerve stimulation on the hormonal balance. These hormones play an important role in humans f.i. the regulation of inflammation. The vagal nerve stimulation can affect the secretion of those hormones and via this pathway inhibiting inflammation.

Study objective

Primary Efficacy Objective
The primary efficacy objective is to determine the long term efficacy of vagal nerve stimulation as assessed by the DAS28 score.

Secondary Efficacy Objectives
The secondary efficacy objectives are to determine the long term efficacy of

vagal nerve stimulation as assessed by:
• the American College of Rheumatology (ACR) 20, 50 and 70 response rate,
• the European League Against Rheumatism (EULAR) response rate, and
• changes in the Euro-QoL EQ-5D quality of life instrument score.

Safety Objectives
The safety objectives are to determine the long term safely of vagal nerve stimulation as assessed by the subject incidence rates of:
• Adverse events
• Serious adverse events
• Device deficiencies

In this hormone and metabolic substudy the effect of vagal nerve stimulation on the secretion of neuroendocrine and metabolic hormones will be studied. Also the effect of food intake will be investigated.

Study design

This will be an open label multicenter study of the safety and efficacy of an active implantable VNS device in patients with rheumatoid arthritis.
Patients who complete study SPM-005 will be enrolled in this study at the time of the last visit of the preceding study. The assessments at the last visit of the preceding study will also be used as baseline measures for the current study. If the patient has previously discontinued SPM-005 and greater than 30 days have elapsed since the final visit in SPM-005, baseline measures for the current study will be repeated, and an interim medical history will be taken to assess whether any new medical conditions were diagnosed in the time between studies.

Visit assessments for the current study:
• Physical Exam
• Vital signs
• RA Disease Assessment
• Euro-QOL Instrument
• Adverse Events
• Concomitant Medications

Custom Diagnostics should be performed prior to discharge from the clinic. Prior to discharge from clinic the patient*s device settings and daily frequency of stimulation sessions (i.e., QD or QID) should be set to the same as those which were being used at the final visit of study SPM-005. The Normal Mode Output Current should remain at 0.0 mA. Throughout the current study, the patient will self-deliver stimulations.

From visit 3 onwards and at the discretion of and after discussion between the Investigator and the Medical Monitor, based on level of RA activity at the visit, stimulation parameters that may be increased or decreased. Allowable

ranges for new parameters are as follows:
• Magnet Mode Output Current: Minimum 0.250 mA, maximum 2.0 mA
• Pulse width 250 microseconds, frequency 10 Hz
• Magnet Mode stimulation time one minute, with a maximum of 5 one minute magnet mode activations per stimulation session, these individual activations to be given over 10-15 minutes
• Stimulation session frequency: Minimum once every two weeks, maximum ten times daily
.

The study will continue until the last patient entered has completed 24 months in this study.

Hormone and metabolic sunstudy:
Patients will fast overnight and will have two visits. One visit with vagal nerve stimulation and food intake and the other without stimulation. The following samples/measurements will be performed:
- blood samples will be drawn on several time points
- resting energy expenditure
- heart rate variability and core temperature

Intervention

The patients will continue to use their previously implanted Cyberonics device for this study.

Study burden and risks

What are the general risks of participating in this research study?

Stimulation of your vagus nerve with the device may cause all, some or none of the adverse events listed below:
symptoms of the throat including hoarseness, voice changes, throat pain, and swallowing difficulties, as well as shortness of breath, nausea, and indigestion. In those patients, these symptoms generally occurred only during the time the device was actually delivering electrical stimulation.

Other uncommon side effects reported include:
• slowing or other alterations of the heart rate,
• scarring or infections of the tissues around where the device is placed,
• worsening of certain lung and breathing diseases such as asthma, chronic obstructive pulmonary disease and sleep apnea in patients who already had these diseases when the device was placed.
• The device itself can move from where it was placed by the surgeon, and this might do damage to the vagus nerve, other nerves, blood vessels or other structures of the body.

• The device or any of its parts can break, in which case it may not deliver stimulation correctly.

Risks relating to surgical removal of the device

At the end of the study the device can be left in place and turned off so it does not deliver electrical stimulation. However, at any time during this study you can decide to have it surgically removed. The device might also need to be removed if it becomes infected and the infection does not respond to antibiotics, or if the device malfunctions in a way that might be dangerous to you. The kinds of complications listed above for surgical implantation can also occur during removal. However, because some scarring around the components of the device usually happens over time, removal carries a higher risk of complications than implantation.

Due to the vena puncture a bruise can occur, which will resolve spontaneously.

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

Patients must have participated in study SPM-005, including patients who either completed that study or withdrew before completion of that study.

Exclusion criteria

Inability to provide informed consent;Significant psychiatric illness or substance abuse

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-02-2012
Enrollment:	13
Type:	Actual

Medical products/devices used

Generic name:	Cyberonics VNS System
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	16-02-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL38631.018.11