A Multicenter, Randomized, Double-Blind, Sham-Controlled Clinical Investigation of the EndoStim® Lower Esophageal Sphincter (LES) Stimulation System for the Treatment of Gastroesophageal Reflux Disease (GERD)

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To demonstrate the safety and effectiveness of the EndoStim® Lower Esophageal Sphincter (LES) Stimulation System in the treatment of subjects with gastroesophageal reflux disease (GERD)

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

Summary

ID

NL-OMON45265

Source
ToetsingOnline

Brief title
CS 100

Condition

- Gastrointestinal disorders

Synonym
acid reflux, Gastroesopahegeal Reflux Disease (GERD)

Research involving

Human

Sponsors and support

Primary sponsor: Clinical Research
Source(s) of monetary or material Support: EndoStim

Intervention

Keyword: Acid Reflux, EndoStim, Gastroesophageal Reflux Disease

Outcome measures

Primary outcome

Safety Endpoint: Rate of occurrence of device- and/or procedure-related serious adverse events at the 12-month follow-up visit as adjudicated by the Data Safety Monitoring Board with a sufficient level of precision

Efficacy Endpoint: Comparison between treatment and control group of percentage (%) of subjects achieving pH success defined as a normalization (distal esophageal pH < 4 for no more than 5.3% of monitoring time) or > 50% improvement in their distal esophageal pH at 6 months compared to their baseline distal esophageal pH performed after at least 5 days off PPIs and at least 2 days off H2 blocker.

Secondary outcome

Secondary Endpoint

Patient-Focused

Number of subjects achieving GERD symptom success defined as an improvement in their composite GERD-HRQL score of 50% or more after 12 months of stimulation compared to their baseline off-PPI or H2 blocker composite GERD-HRQL score.

Secondary Endpoints, Blinded Phase (comparison between Treatment and Control Groups at the 6-month follow-up visit).

Change from baseline to the 6-month follow-up visit of the mean percentage (%) of time distal esophageal pH is <4.0 using Bravo Esophageal pH Monitoring performed after at least 5 days off PPIs and at least 2 days off H2 blocker

Heartburn symptom frequency and severity (day and night) as measured by Subject Diary

Mean acid-suppression (PPI and H2 blocker) medication use

Regurgitation symptom frequency and severity (day and night) as measured by Subject Diary

Mean Quality of life scores as measured by SF-12

Secondary Endpoints, Open-Label Treatment Phase (comparison between baseline data and after 12 months of stimulation where each subject serves as its own control)

Mean percentage (%) of time distal esophageal pH is <4.0

Number of subjects reporting 50% or more reduction in severity of heartburn symptoms as measured by daily Subject Diary

Number of subjects reporting 50% or more reduction in severity of regurgitation symptoms as measured by daily Subject Diary

Number of subjects able to stop regular use of acid-suppression medication (defined as 50% or more Subject Diary days without PPI use)

Number of subjects able to stop all use of acid-suppression medication (defined as 100% Subject Diary days without PPI use)

Number of subjects reporting 50% or more reduction in nocturnal symptoms of heartburn as measured by daily Subject Diary

Number of subjects reporting 50% or more reduction in nocturnal symptoms of regurgitation as measured by daily Subject Diary

Number of subjects achieving symptom success compared to PPI defined as an improvement in their composite GERD-HRQL score of 50% or more compared to their baseline on-PPI or H2 blocker composite GERD-HRQL score

Mean quality of life scores as measured by SF-12

Study description

Background summary

BACKGROUND AND JUSTIFICATION
Gastroesophageal Reflux Disease (GERD) is a common problem affecting 14-17% of the population in the United States (US). Approximately 250 million subjects worldwide and 30 million subjects in the US suffer from GERD. Among the 12 million Americans who suffer from daily heart-burn (the main symptom of GERD) almost 5 million do not respond completely to medications and many more do not want or cannot take medications due to side-effects. The total annual cost of care of GERD in the US is estimated at $9.8 billion, $5.8 billion of which are spent on medication.1
The goals of treatment in GERD are to relieve symptoms, heal esophagitis if present, prevent recurrence of symptoms and esophagitis, and prevent complications. Medical acid-suppressive therapy with proton pump inhibitors heals esophagitis, relieves symptoms and improves quality of life. However, acid suppressive therapy does not correct the underlying pathophysiology of dysfunction lower esophageal sphincter and hence symptoms of reflux due to weakly acidic or non-acid reflux persist in the majority of subjects. Recent reports about the safety of long-term proton pump inhibitors and drug interactions have raised concerns about safety of these drugs.2
Prior endoscopic techniques for the treatment of GERD may be categorized into 3 groups: (1)
sewing/plication at the cardia and gastroesophageal (GE) junction, (2) radiofrequency (RF) thermal therapy to the lower esophageal sphincter (LES), and (3) injection/implantation of biopolymers at the GE junction. Minimally invasive endoluminal procedures for GERD are designed to provide long-lasting

symptom relief and abolish or lessen medication dependency. Most endoluminal modalities that were introduced into clinical practice have failed due to lack of efficacy or due to complications.3 Surgical therapy decreases symptoms and improves the quality of life in GERD; however, there remain concerns regarding postoperative adverse events and the durability of the surgical procedure. The results reported from operations performed in community hospital lower-volume centers have been different than those achieved in centers of excellence. It has been reported that between 23% and 62% of patients who have undergone laparoscopic Nissen fundoplication use acid suppression medications at long-term follow-up. Due to these issues patient and physician acceptance of surgical procedures remains low and is mainly limited to patients with severe GERD or those non-responsive to medications.4-8
Abnormalities in the structure and function of the LES, such as hypotensive LES or inappropriate transient LES relaxation (t-LESR) may predispose patients to GERD, making the LES the ideal target for therapy. Recent reports in animals have suggested that electrical stimulation of the LES results in an increase in the LES pressure and restoration of normal LES function.9-12
EndoStim has developed a medical device specifically designed to deliver electrical stimulation to the LES. The results of EndoStim clinical feasibility studies suggested that, in GERD subjects, LES electrical stimulation therapy is a safe, and likely an effective method for treating GERD by enhancing LES tone and restoring normal LES function, which results in significant and sustained improvement in GERD symptoms, reduction in esophageal acid exposure , reduction in GERD medication use and improvement in patients* quality of life.13-19
Results of these ongoing studies are promising and warrant additional clinical studies, including a sham-controlled study, to evaluate the safety and effectiveness of the EndoStim LES Stimulation System to treat GERD.

Study objective

To demonstrate the safety and effectiveness of the EndoStim® Lower Esophageal Sphincter (LES) Stimulation System in the treatment of subjects with gastroesophageal reflux disease (GERD)

Study design

A multicenter, randomized, double-blind, sham-controlled study.
All subjects undergo screening and baseline visits, followed by system implantation, and randomization to either a Treatment Group (immediate stimulation) or Control Group (delayed stimulation).
Randomized subjects complete a 6-month, double-blind phase.
At the 6-month visit, subjects are unblinded, Control Group subjects begin receiving stimulation, and are followed for an additional 12-month open-label treatment phase and Treatment Group subjects continue treatment for an additional 6 months.
Subjects continue receiving stimulation for an extended follow-up phase

involving a phone interview 18 months post stimulation and annual visits through 5 years.

Intervention

Bravo Esophageal pH Monitoring
Esophageal Manometry (HRM)
Endoscopy
12-Lead ECG Monitoring
Laparoscopy and System Implantation, ECG Monitoring
Urine Pregnancy Test
HbA1c
Chem7 or Basic Metabolic Panel
Complete Blood Count

Study burden and risks

Results from this study could validate a new, minimally invasive therapy for the effective treatment of GERD. If proven effective, the therapy could provide the subject with improved LES function and reduced symptoms of GERD and therefore reduce or eliminate the need for acid suppressive therapy or other more invasive treatment.
Potential Increased Risk Analysis
The potential adverse events and risks associated with this study and the use of the LES Stimulation System are identical to those normally associated with standard gastrointestinal stimulation therapy or an invasive, clinical procedure (e.g. IPG and electrode placement, etc.).
Specific risks associated with the implantation procedure include: Infection or fever, allergic reaction, pain or discomfort, perforation, tissue abrasion / erosion, cardiac arrhythmia, cardiopulmonary depression, complications (pain, phlebitis/ infection) associated with the intravenous canula insertion, aspiration pneumonia, hematoma, seroma, wound separation, risks associated with laparoscopy and the use of anesthesia/sedatives.
Laparoscopy risks include but not limited to unstable blood pressure, vertigo, swelling, injury to organs, blood vessels or other structures and internal bleeding.
Anesthesia risks include but are not limited to nausea, vomiting, fever, hypoxia, pneumonia, adverse drug reactions, urine retention, clumsiness, drowsiness, blurred vision and death.
Potential risks associated with the LES electrical stimulation therapy include: chest pain or discomfort, abdominal pain or discomfort, worsening of GERD symptoms, and dysphagia or odynophagia.
There is a potential that any system component could malfunction, become damaged, infected, or, in the case of the leads, become dislodged or fractured. System component malfunction or other clinical circumstances (eg, sepsis) may require noninvasive corrective actions or possibly even a surgical revision

(repositioning, replacement, or removal) of the malfunctioning component(s). Risks associated with the implant procedure are mitigated by selection of experienced laparoscopic surgeons and providing detailed training on the EndoStim implantation procedure. Risks associated by adverse effects of the electrical stimulation are mitigated by EKG monitoring during the first stimulation session of each patients. No stimulation related adverse events have been encountered thus far in prior clinical trials.
The potential adverse events and risks associated with this study and the use of the LES Stimulation System are identical to those normally associated with standard gastrointestinal stimulation therapy or an invasive, clinical procedure (e.g., IPG and electrode placement, etc.).
In relation to the physiological assessment techniques:
Manometry and pH testing procedure
Although manometry and pH testing is commonly used to assess GERD, there are possible risks associated with this procedure. The patients may experience pain or discomfort when the manometry or pH tube is placed in the oesophagus. The patients will be given a local anaesthetic to prevent any pain or discomfort. The patient may also experience retching or vomiting which could increase the risk of aspirating a food particle into the lungs. There is a small chance that this could lead to sinusitis or pneumonia. To ensure that no food particles are present in your stomach that could be aspirated into the lung, the patients will fast prior to manometry tube placement.
Endoscopy
Endoscopy is generally a safe procedure, however complications can occur. There is a risk of bleeding if a piece of tissue was removed for testing. If a piece of tissue was removed, there is a risk of tearing (perforation) through the upper digestive tract. This may require hospitalisation and sometimes surgery to repair it. There is also a risk of an infection in the part when endoscopes are used for the examination. In order to treat the infection, the patient will usually be prescribed antibiotics which are a common treatment.
Risks to Pregnancy
The risks of implanting the EndoStim device in a pregnant woman are unknown. Pregnant women may not take part in this research trial. Women with child bearing potential will only be considered as potential candidates if they have been on two forms of effective contraception for the last three months and are committed to keep using oral contraception throughout the study, and/or for as long as they have the EndoStim device implanted. Women who plan to become pregnant during the study may not participate.
Trained staff will undertake the management of any adverse effects. The facilities where subjects will be assessed are fully equipped for emergency situations.

Contacts

Public
Selecteer

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subject is 22 * 75 years of age at the time of informed consent
Subject with documented symptoms of GERD for longer than 6 months (regurgitation and/or heartburn which is defined as burning epigastric or substernal pain which responds to acid neutralization or suppression) which requires daily use of proton pump inhibitors (PPIs) or other antireflux drug therapy, who continue to have symptoms despite maximum medical therapy or are *intolerant* severe
sideeffects (e.g. anaphylaxis or severe allergic reaction, recurrent C. difficile, severe hypomagnesaemia) to one PPI or mild/moderate side effect (e.g.
nausea, vomiting, diarrhea or abdominal pain) to at least 2 PPIs of different chemical classes.
Subjects with symptomatic improvement on PPI therapy demonstrated by a composite GERDHRQL score of *20 off PPI, and with *10 point improvement on PPI when comparing to their off PPI composite GERDHRQL score.
Subject has exhibited excessive lower esophageal acid exposure during pH monitoring (defined as distal esophageal pH < 4 for > 6.0% of the monitoring time) performed after at least 5 days off of PPIs and at least 2 days off of H2 blockers.

Subject has esophagitis * Grade B (LA classification) as measured by upper endoscopy off PPI and H2 blockers for at least 10 days.

Exclusion criteria

Exclusion Criteria
Subjects must not meet any of the following study exclusion criteria:
a. Subject had a previous EndoStim LES System implant and/or implant attempt
b. Subject underwent previous surgery involving the gastroesophageal junction or the lead implant site, such as a Nissen fundoplication
c. Subject underwent previous endoscopic intervention for the treatment of GERD and/or Barrett*s esophagus
d. Subject has a hiatal hernia larger than 3 cm as determined by endoscopy
e. Subject has history of gastroparesis
f. Subject has any nonGERD esophageal motility disorders that in the opinion of investigator precludes an antireflux procedure
g. Subject has history of or known esophageal stricture or significant esophageal anatomic abnormalities (obstructive lesions, etc.)
h. Subject has Barrett*s esophagus or any grade of dysplasia
i. Subject has documented history of esophagitis Grade C or D (LA Classification)
j. Subject has a history of suspected or confirmed esophageal or gastric cancer
k. Subject has esophageal or gastric varices
l. Subject has symptoms of dysphagia more than once per week every week within the last 3 months
m. Subject is unable to tolerate withdrawal from H2 Blockers or PPI medications
n. Subject has suspected or known allergies to titanium, platinum, iridium, stainless steel, silicone, epoxy, or nylon
o. Subject has a body mass index (BMI) > 35 kg/m2
p. Subject has any significant multisystem diseases
q. Subject has an autoimmune or a connective tissue disorder (scleroderma, dematomyositis, CalcinosisRaynaud*sEsophagus Sclerodactyly Syndrome (CREST), Sjogren*s Syndrome, Sharp*s Syndrome, etc.) requiring therapy in the preceding 2 years
r. Subject has Type 1 diabetes mellitus or uncontrolled Type 2 diabetes mellitus (T2DM) defined as HbA1c > 9.5 in the previous 6 months or at screening/baseline
s. Subject has significant cardiac arrhythmia or ectopy or significant cardiovascular disease (i.e. unstable angina pectoris, hemodynamically significant valvular disease, severe congestive heart failure), or any cardiac therapeutic intervention within the last 6 months.
t. Subject has had a significant cerebrovascular event within the last 6 months
u. Subject has an existing implanted electrical stimulator (pacemaker, implantable cardioverter defibrillator, DBS, bone growth or pelvic floor stimulators, drug pumps, etc.)
v. Female subject of childbearing potential and is pregnant or nursing, or intends to become pregnant during the trial period, who is not using a reliable form of birth control
w. Subject is currently enrolled in other potentially confounding research
x. Subject has an active infection as determined by the investigator
y. Subject has a history of any malignancy in the last 2 years

z. Subject has a life expectancy less than 3 years
aa. Subject has a diagnosed major psychiatric disorder (bipolar, schizophrenia, etc.)
bb. Subject has any condition that, at the discretion of the investigator or sponsor, would interfere with accurate interpretation of the study endpoints or preclude participation in the trial

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-03-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	EndoStim® Lower Esophageal Sphincter (LES) Stimulation System
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	08-08-2017
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NCT02749071
CCMO	NL58772.091.16