An Investigation of the Effect of Long-Term Electrical Stimulation on Lower Esophageal Sphincter (LES) Pressure and Esophageal Acid Exposure in Patients with Gastroesophageal Reflux Disease (GERD)

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Primary Safety Endpoint:Safety will be assessed by incidence and severity of adverse events through 12-weeks (3 month) follow-up. Included in this assessment will be the proportion of subjects with any of the following outcomes between device...

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

Summary

ID

NL-OMON35885

Source
ToetsingOnline

Brief title
CS005, EndoStim Inc., Electrical Stimulation

Condition

- Other condition

Synonym
Gastroesophageale Reflux Disease and Reflux Disease

Health condition

Thoracic disorders: Reflux Disease

Research involving
Human

Sponsors and support

Primary sponsor: EndoStim, Inc.
Source(s) of monetary or material Support: EndoStim;Inc.

Intervention

Keyword: Electrical Stimulation, EndoStim Inc., Gastroesophageal Reflux Disease, Lower Esophageal Sphincter

Outcome measures

Primary outcome

Primary Safety Endpoint:

Safety will be assessed by incidence and severity of adverse events through 12-weeks (3 month) follow-up. Included in this assessment will be the proportion of subjects with any of the following outcomes between device implant and completion of the Week 12 evaluation: (1) death, or (2) medical morbidity associated with the device and/or implantation procedure, including cardiac arrhythmias, pneumonia, wound infection, IPG or lead perforation, or significant lead dislocation requiring hospitalization. Safety variables will be tabulated and presented for all patients in the treatment group. Number of patients undergoing device implantation and any reasons for discontinuation of study treatment will be tabulated

Primary Functionality Endpoint: functionality will be assessed by the ability of the device to initiate stimulation as programmed and to accurately detect the patient*s posture. Indication of device detection when the patient is

lying horizontally and when standing up will be recorded.

Secondary outcome

Secondary Efficacy Endpoints:

1. Change in patient*s GERD-HRQL from baseline (as measured while off PPI) to 3 months.

2. The baseline LES end expiratory pressure (LESPpre) and the on-stimulation LES end expiratory pressure (LESPpost) at three months.

3. The baseline pH values of % 24-hour esophageal pH< 4.0, and number of reflux events >1minute and >5 minute duration with the same on-stimulation pH parameters at three months.

4. Baseline symptoms as measured by patient symptom diary and patients quality of life measured by SF-12 with on-stimulation symptoms and QOL at three months.

5. Decrease in antisecretory medication use compared to baseline.

Study description

Background summary

Gastroesophageal Reflux Disease (GERD) is a common problem affecting approximately 250 million patients worldwide and 30 million patients in the US suffer from GERD. Among the 12 million Americans who suffer from daily heartburn (the main symptom of GERD) almost 5 million do not respond to any medications and many more do not want or cannot take medications due to risk or side-effects. These patients have few satisfactory alternatives, and almost 50-100,000 of these patients choose to undergo a major surgical procedure, Nissen fundoplication, each year. The goals of treatment in GERD are to relieve symptoms, heal esophagitis if present, and prevent recurrence of symptoms and complications. Medical acid-suppressive therapy with PPI heals esophagitis, relieves symptoms and improves quality of life. However, acid suppressive therapy does not correct the underlying pathophysiology and hence symptoms of reflux persist in the majority of patients. 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. 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. 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. EndoStim has developed an investigational medical device specifically designed to deliver electrical stimulation to the LES and has completed two clinical feasibility studies using an external version of the EndoStim stimulation system in fifteen subjects. In these two studies, acute, short-term electrical stimulation resulted in significant increases in LES pressure with no adverse effects reported. Results of these studies are promising and warrant additional clinical study to evaluate the effectiveness of EndoStim stimulation system to treat GERD over time.

Study objective

Primary Safety Endpoint:
Safety will be assessed by incidence and severity of adverse events through 12-weeks (3 month) follow-up. Included in this assessment will be the proportion of subjects with any of the following outcomes between device implant and completion of the Week 12 evaluation: (1) death, or (2) medical morbidity associated with the device and/or implantation procedure, including cardiac arrhythmias, pneumonia, wound infection, IPG or lead perforation, or significant lead dislocation requiring hospitalization. Safety variables will be tabulated and presented for all patients in the treatment group. Number of patients undergoing device implantation and any reasons for discontinuation of study treatment will be tabulated
Primary Functionality Endpoint:
Functionality will be assessed by the ability of the device to initiate stimulation as programmed and to accurately detect the patient*s posture. Indication of device detection when the patient is lying horizontally and when standing up will be recorded.

Secondary Efficacy Endpoints:
1. Change in patient*s GERD-HRQL from baseline (as measured while off PPI) to 3 months.
2. The baseline LES end expiratory pressure (LESPpre) and the on-stimulation LES end expiratory pressure (LESPpost) at three months.

3. The baseline pH values of % 24-hour esophageal pH< 4.0, and number of reflux events >1minute and >5 minute duration with the same on-stimulation pH parameters at three months.
4. Baseline symptoms as measured by patient symptom diary and patients quality of life measured by SF-12 with on-stimulation symptoms and QOL at three months.
5. Decrease in antisecretory medication use compared to baseline.

Study design

Screening
The Investigator will determine if the patient is eligible to participate in this study. Within two to four weeks prior to the scheduled laparoscopic study procedure to implant the investigational device, the patient will see the study doctor to complete baseline tests. The patient will be taken off of any acid suppressive therapy 5-14 days prior to this baseline testing visit and remain off the medications until after completion of baseline testing. While the patients are off of these medications, they will be permitted to use antacids on an as-needed basis to reduce any GERD symptoms they experience. The baseline tests include a physical examination, a blood test, EKG test to assess patients* heart*s function, and endoscopy to examine the interior of the patients* esophagus. The patient will be asked to complete a questionnaire regarding the severity of their GERD symptoms. The severity of the patients* GERD symptoms and the function of patients* esophagus will also be assessed using esophageal manometry. Esophageal manometry measures the strength and muscle coordination of patients* esophagus when the patient swallows. During the manometry test, a tube is passed through the patients* nose, along the back of the throat, down the esophagus and into the stomach. The tube does not interfere with their breathing. The tube is connected to a machine that records the contractions of the esophageal muscles on a graph. The patient will be asked to not eat or drink anything eight hours prior to the manometry test. A topical anesthetic (pain-relieving medication) may be applied to the patients* nose to make the passage of the tube more comfortable. At this time, the doctor will also place pH capsule or tube in the patients* esophagus to measure the acidity level. The pH tube is passed through the patients* nose or mouth, along the back of the throat, down the esophagus and into the stomach and left in place, until it passes. A data recorder is worn on the patients* belt and records the pH data from their esophagus. If the pH capsule is used, it will be placed using a catheter that is swallowed. The capsule is attached to the esophageal lining and the catheter is then removed. The capsule records the pH data from the patients* esophagus for 24-48 hrs. The next day the patient will return to see the doctor at which time the data recorder will be removed. If a capsule is used, it will fall off in 7-10 days and naturally passes in the stool. If a tube is used, it will be removed the same time the data recorder is returned. The patient will also be asked to complete antacid use and symptoms diary.
The next day the patient will return to see the doctor at which time the data recorder and the pH tube will be removed.

If the patient underwent endoscopy, manometry or pH-metry any time within the last 6 months prior to enrollment to the study, the results of these tests can be used as their baseline and there will be no need to repeat them for the baseline evaluation. If, at any time during the study (in the opinion of the patients* physician), the results of manometry or pH tests are compromised due to noncopliance or equipment malfunction, the relevant test(s) may be repeated.

Implantation procedure
At the time that the patients are admitted into the hospital for the laparoscopic study procedure, a study doctor will perform a physical examination, a blood test, an EKG and endoscopy test prior to surgery. During the laparoscopic study procedure, the study doctor will attach the investigational device, called a stimulation lead, to the lower part of the patients* esophagus. The study doctor will also place a small battery-operated electrical stimulator, much like a pacemaker, in the patients* abdomen. The stimulation lead will then be connected to the electrical stimulator so that electrical energy can be delivered to the esophagus. After surgery, the patients will stay in a hospital for a day or two until they recover. During the first day after surgery, the study doctor will monitor the patients* condition. Once the patients have recovered from the surgery, the study doctor will turn on the investigational device and initiate the investigational therapy. The doctor will monitor the patients* heart condition upon starting the therapy and observe how the patients are responding. Once the doctor determines it is safe for the patient to go home, the patient will be discharged from the hospital.

Therapy adjustment and Follow-up
From this point until the patient complete the study, the patient will receive investigational therapy (electrical stimulation to their lower esophagus) in place of any acid suppressive therapy the patient may have been receiving. The patients are permitted to take antacids to relieve any GERD symptoms the patient experience while receiving the investigational therapy. The patients will be asked to keep a diary to track their antacid use and symptoms while they are participating in the study.

Approximately two weeks after being discharged from the hospital, the patient will return to the investigator*s office for follow-up. The patients will be asked to complete questionnaires regarding their GERD symptoms and their device will be checked to make sure it is functioning properly.
The patient will be asked to return to the study doctor*s office periodically for evaluation. The patients will return to the study doctor*s office approximately one month, three months and six months after the implant. The patients will be asked to fast for at least 8 hours prior to their visits.
These follow-up visits are much like the baseline visit they received prior to the surgical procedure. At these visits, the patient will receive a physical

examination, a blood test, an EKG test to assess the patients* heart function (only at the 3 months visit) and endoscopy (only at the 3 months visit). The patients will be asked to complete questionnaires regarding the severity of their GERD symptoms. The severity of their GERD symptoms and the function of the patients* esophagus will also be assessed using 24-hour esophageal manometry and pH tests. The manometry tube and pH tube or capsule is placed into the patients* esophagus and a data recorder attached to their belt. The next day the patient will return to see the doctor at which time the data recorder, manometry tube, and pH tube or capsule, will be removed. Video recordings may be taken. Any (fluoroscopic, xray or video) images will be confidential and used only by the study doctor or the study sponsor (EndoStim) to document the research session. In each of these visits the device will be checked to assure that it is working properly.

The study doctor*s office will also contact the patient on the telephone each month that the patients are not scheduled for a visit (two, four and five months after the implant) to ensure the patients are not experiencing any complications. During the phone call, the doctor*s office will evaluate how the patient is doing and ask questions to evaluate their GERD symptoms. If the patient is experiencing any issues or has any questions or concerns, the patient is asked to notify the study doctor during their next phone call or follow up visit.

Post study
At the end of the study (approximately six months after the implantation procedure), the patients will meet with their study doctor to discuss whether the device should be removed. The decision will be based on the doctor*s opinion and the patients* evaluation of the extent to which the patient has benefitted from the device. If, at the discretion of the study doctor, a decision has been made to remove the device, a date will be set when the patient will be admitted into the hospital for removal of the investigational device. Once the patient has recovered, the study doctor will discharge the patient home. The patient will be asked to return to the doctor*s office approximately one week later for a follow-up evaluation to ensure the patient is not experiencing any complications. This will complete the patient participation in the study. If the device is not removed, the patients will be asked to return to the hospital for follow up approximately every three months.

Any test samples obtained during this study will be only for the purpose of this present study. The samples will not be stored for any use other than this research study and will be identified by the patients* study ID and not by the patient*s name.

Intervention

Laparoscopy:
During the laparoscopic study procedure, the study doctor will attach the

investigational device, called a stimulation lead, to the lower part of the patients* esophagus. The study doctor will also place a small battery-operated electrical stimulator, much like a pacemaker, in the patients* abdomen. The stimulation lead will then be connected to the electrical stimulator so that electrical energy can be delivered to the esophagus.

Study burden and risks

Results from this study could lead to the development of 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.
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.).

Any new medical device or procedure may have unknown, as well as known, side effects, discomforts and risks. The following side effects are possible if you take part in this study.

There is a small chance that you may develop an infection or fever from the procedures used in this research study including the laparoscopic procedure to implant and remove the investigational device. All of the instruments that contact you will be sterilized and used in a sterile setting using adequate techniques for laparoscopic procedures. Additionally, you may be given antibiotics prior to the procedure as a preventative measure. Following the procedure, a physician or nurse will do a visual examination of the incision in your abdomen to look for any signs of bleeding, redness, inflammation or discharge, and you may be treated with antibiotics if needed. Likewise, your temperature will be monitored for a fever and you may be treated with acetaminophen or ibuprofen if needed.

There is a potential that any system component could malfunction, become damaged, infected, or, in the case of the leads, become dislodged. Malfunction of any of these components or other clinical circumstances (e.g., sepsis) may require noninvasive corrective actions or possibly even a surgical correction (repositioning, replacement, or removal) of the malfunctioning component(s).

As with any procedure, there is a small chance that you may have an allergic reaction or other unanticipated reaction to the materials or medications used in this research study.
You may develop unanticipated adverse reactions to the medications used for sedation or anesthesia and control of discomfort or pain. These medications have been used for many years and rarely cause serious problems, but there is a potential for a harmful side effect including decreased blood pressure, nausea,

vomiting, seizures, hallucinations, allergic reaction, skin rash, fever, or cardiac arrhythmia (irregular heartbeats) and respiratory depression (slowed breathing). Cardiac arrhythmia may rarely lead to cardiac arrest, coma or death. If respiratory depression occurs, your breathing could rarely slow to a dangerous level or even stop. This could require that a breathing tube be temporarily inserted while the medication wears off, or longer, if necessary. The discomforts of the sedatives / anesthesia include possible headaches or a sore throat and aspiration pneumonia (inflammation of the lungs and airways to the lungs from breathing in foreign material).

You may develop unanticipated adverse reactions to the laparoscopic procedure including hematoma, seroma and wound separation. You will be monitored after the procedure to ensure that any complications are promptly and appropriately treated prior to your discharge home.

Although manomtetry is commonly used to assess GERD, there are possible risks associated with this procedure. You may experience pain or discomfort when the manometry tube is placed in your esophagus. Your doctor will give you a local anesthetic to prevent any pain or discomfort. You may also experience increased salivation which could increase your risk of breathing a food particle into your lungs. There is a small chance that this could lead to pneumonia. To ensure that no food particles are present that could be breathed in, you will fast before the manometry tube is placed each time.

You may experience pain or discomfort resulting from the electrical stimulation delivered by the investigational device. If at any time you experience pain or discomfort, the doctor will modify the electrical stimulation parameters or discontinue delivery of the electrical stimulation and prescribe medications to alleviate the pain if needed.

There is a small chance that the investigational device could cause a small hole in your esophagus, called a perforation. The doctor will secure the investigational device at the time of surgery to ensure that it will not become loose and lead to a perforation. Also, the doctor will be checking the investigational device periodically throughout the entire study to ensure that it will not become loose. If the investigational device causes a perforation, it maybe treated with antibiotics alone or a surgery may be required to close the hole and prevent any further complications.

There is a small chance that the investigational device could lead to irregular or abnormal electrical activity in your heart. Such an irregularity is called a cardiac arrhythmia. To ensure that your heart is not experiencing cardiac arrhythmia, the doctor will use EKG, a device to monitor your heart*s electrical activity, at the study visits.
All these potential risks are treatable, and if treated timely, your life should not be at risk. Your doctor will discuss with you all the signs and

symptoms so that you pay attention to them. If you experience any of the signs and symptoms discussed with your doctor, call him immediately and he will tell you if you should go to a hospital for any treatment.

There may be other device-related problems that are not known yet. If you receive the EndoStim device you will be notified of any new risks that become known during the study that may affect your decision of whether to continue in the study.

Risks to Pregancy
The risks of implanting the investigational device in a pregnant woman are unknown. Pregnant women may not take part in this research trial.

Child bearing age women could only be considered as potential candidates if they underwent surgical sterilization or have been on oral 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.

Contacts

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US
Scientific
EndoStim, Inc.

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

a. Subject is between 21 - 65 years of age.
b. Subject has a history of heartburn, regurgitation or both for >6 month prompting physician recommendation of continual daily use of PPI before study entry. Baseline GERD HRQL heartburn score of >= 20 off PPI assessed during the run in phase.
c. Subject has an American Society of Anesthesiologists (ASA) Physical Status Classification I or
II (or comparable local classification if any).
d. Subject has demonstrated satisfactory symptomatic response to a previous course of GERD
therapy (>= 2 weeks). GERD HRQL heartburn score improvement of > 10 on therapy as assessed within 6 weeks of enrollment.
e. Subject has exhibited excessive lower esophageal acid exposure during 24-hour pH-metry of
antisecretory therapy performed within 6 months of enrollment; pH < 4 for > 5% of total time or >
3% of supine time.
f. Subject has a resting LES end expiratory pressure > 5mm Hg and < 15 mm Hg on a high resolution manometry within 6 months of enrollment.
g. Subject has esophagitis <= Grade C (LA classification) on upper endoscopy within 6 months of
enrollment.
h. Subject has esophageal body contraction amplitude > 30 mmHg for >70% of swallows and >
50% peristaltic contractions on high resolution manometry.
i. Subject has signed the informed consent form.

Exclusion criteria

a. Subject has any non-GERD esophageal motility disorders.
b. Subject has gastroparesis.
c. Subject has any significant multisystem diseases.
d. Subject has an autoimmune or a connective tissue disorder (e.g. scleroderma, dematomyositis, Calcinosis-Raynaud*s-Esophagus Sclerodactyly Syndrome (CREST), Sjogren*s Syndrome, Sharp*s Syndrome) requiring therapy in the preceding 2 years.
e. Subject has Barrett*s epithelium (> M2; >C1) or any grade of dysplasia.

f. Subject has a hiatal hernia larger than 3 cm.
g. Subject has a body mass index (BMI) greater than 35 kg/m2.
h. Subject has Type 1 diabetes mellitus
i. Subject has uncontrolled Type 2 diabetes mellitus (T2DM) defined as HbA1c >9.5 in the previous 6 months, or has T2DM for > 10 years.
j. Subject has a history of suspected or confirmed esophageal or gastric cancer.
k. Subject has esophageal or gastric varices.
l. Subject has significant cardiac arrhythmia or ectopy or significant cardiovascular disease.
m. Subject has an existing implanted electrical stimulator (e.g., pacemaker, AICD).
n. Subject requires chronic anticoagulant therapy.
o. Subject has dysphagia or esophageal peptic stricture, excluding Schatzki*s ring.
p. Subject is pregnant or intends to become pregnant during the trial period.
q. Subject is currently enrolled in other potentially confounding research.
r. History of any malignancy in the last 2 years.
s. History of previous esophageal or gastric surgery, including nissen fundoplication.
t. Subject has any condition that, at the discretion of the investigator or sponsor, would preclude
participation in the trial.

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Generic name:	EndoStim LES Stimulation System
Registration:	No

Ethics review

Approved WMO Date:	19-09-2011
Application type:	First submission
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	NL35769.041.11