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)

Clinical Investigational Plan

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CLINICAL INVESTIGATIONAL PLAN
SIGNATURE PAGE

I have received a copy of and have reviewed this clinical investigational plan and agree to conduct the clinical investigation in accordance with this document, IDE regulations, other applicable regulations of the U.S. FDA for protecting the rights, safety, and welfare of subjects under my care, and any conditions of approval imposed by the reviewing Institutional Review Board or U.S. FDA.

Investigator Name (Printed)

Investigator Signature **Date**

Sponsor Representative Signature

Name (Printed)

Signature **Date**

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1. PROTOCOL SYNOPSIS

Title	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), Protocol # CS-100
Investigational Device	EndoStim® Lower Esophageal Sphincter (LES) Stimulation System
Purpose	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)
Population	Subjects diagnosed with pathological gastroesophageal reflux disease (GERD) as defined by abnormal pH and who continue to have chronic GERD symptoms despite maximum medical therapy for the treatment of reflux or who are intolerant to medical therapy
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 post-stimulation
Sample Size and Scope	• A minimum of approximately 400 subjects will need to be consented to result in 120 implanted subjects followed to 12 months at a maximum of 30 investigational sites globally
Key Subject Selection 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 anti-reflux drug therapy, who continue to have symptoms despite maximum medical therapy or are "intolerant" - severe side-effects (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 listed in Table 4 • Subjects with symptomatic improvement on PPI therapy demonstrated by a composite GERD-HRQL score of ≥20 **off PPI**, and with ≥10-point improvement **on PPI** when comparing to their **off-PPI** composite GERD-HRQL score. The **on-PPI** score to satisfy this criterion will be the score from the GERD-HRQL assessment completed after resuming PPIs following the Baseline visit. Patients who meet the definition above of PPI intolerant are not required to have ≥10-point improvement and are not required to take the GERD-HRQL for inclusion. • 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 PPIs** and at least 2 days **off H2** blockers • Subject has esophagitis ≤ Grade B (LA classification) as measured by upper endoscopy **off PPI** and **off H2** blockers for at least 10 days
Primary Endpoints	• 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 Clinical Events Committee • 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 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 (day and night) and highest level of severity as measured by Subject Diary • Mean acid-suppression (PPI and H2 blocker) medication use • Regurgitation symptom frequency (day and night) and highest level of severity 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 highest level of severity of heartburn symptoms as measured by daily Subject Diary • Number of subjects reporting 50% or more reduction in highest level of 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 post-stimulation compared to previous PPI utilization 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 (not available for PPI-intolerant subjects) • Mean quality of life scores as measured by SF-12
Study Visits	• Screening and baseline visits • Laparoscopic IPG and lead implant procedure • Post-implant follow-up office visits at 2 weeks/randomization, and 1, 3, 6, 9, and 12 months, followed by annual visits through 5 years. There are additional visits at 7, 15, and 18 months for the Control Group. • Follow-up phone interviews post-implant at 2 and 4 months for all subjects, additional phone interviews at 8, 10 and 24 months for Control Group Subjects and at 18 months for Treatment Group Subjects
Sponsor	EndoStim, Inc., 1609 Shoal Creek Blvd., Suite 303, Austin, TX 78701 USA[1]

[1] In Europe, EndoStim B.V. acts as both the manufacturer and legal representative for EndoStim, Inc.

2. INTRODUCTION

The purpose of this investigation is 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). This investigation is a multicenter, randomized, double-blind, sham-controlled clinical investigation that will be conducted at a maximum of 30 investigational sites. All eligible subjects will undergo screening and baseline testing followed by the implant procedure. After the implant procedure, subjects will be randomized to either the Treatment Group (immediate stimulation) or Control Group (delayed stimulation) for a 6-month, double-blind phase followed by an additional open-label treatment phase in which all subjects will receive electrical stimulation therapy for a total of 12 months (Treatment Group subjects undergo stimulation for an additional 6 months and Control Group subjects undergo stimulation for 12 months). Subjects continue on stimulation treatment and an extended open-label follow-up phase includes an 18-month post-stimulation phone interview followed by annual visits through 5 years.

3. 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 heartburn (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 dysfunctional 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.

4. SYSTEM DESCRIPTION

The EndoStim® Lower Esophageal Sphincter (LES) Stimulation System is intended for subjects diagnosed with pathological gastroesophageal reflux disease (GERD) as defined by abnormal pH and who continue to have chronic GERD symptoms despite maximum medical therapy for the treatment of reflux or who are "intolerant" to medical therapy with PPI's. "Intolerance" is defined as those patients who experience severe side effects such as anaphylaxis or a severe allergic reaction, recurrent C. diff, severe hypomagnesaemia to one PPI or experience mild/moderate side effects such as nausea, vomiting, diarrhea or abdominal pain to at least 2 PPIs listed in Table 4. Subjects who are mildly allergic to medical therapy (i.e. rash) would not immediately be considered intolerant and should first be placed on an alternate medical therapy before being considered for EndoStim. The system is intended to improve LES functionality as defined by improved esophageal acid exposure and reduced GERD symptoms.

The EndoStim Lower Esophageal Sphincter (LES) Stimulation System contains three components:

- EndoStim Implantable Pulse Generator (IPG), Part Number 1006, FW v0.12 (Figure 1)
- EndoStim Implantable Bipolar Leads, 10 mm, Part Number 1003 (Figure 2)
- EndoStim Programmer System (Figure 3), comprised of:
    - Tablet PC with EndoStim LES Programmer Software, Part Number 1522
    - EndoStim Programmer USB Wand, Part Number 1504

The EndoStim Implantable Pulse Generator (IPG) is a sterile, single-use device. The IPG casing is made of titanium and contains a medical-grade lithium battery, microelectronics, and communication coils. The battery is used to power the microelectronics, which produce the stimulation energy and communicate with the external programmer via the communication coils. The entire titanium casing is hermetically sealed to prevent damage to the device from biological fluids. The header, or top clear section of the device, is where the lead is inserted and is made of biocompatible epoxy. The epoxy encapsulates stainless steel contacts that are used for

connection to the implantable stimulating lead. These contacts are connected to the microelectronics through the use of feedthroughs that hermetically pass into the titanium casing.

Figure 1. EndoStim Implantable Pulse Generator (IPG)

Main device specifications are provided in Table 1.

Table 1. EndoStim Implantable Pulse Generator (IPG) – Specifications

Description	**Specification**
Height	62 mm
Width	39 mm
Thickness	8.4 mm
Mass	28 g
Biocompatible materials in contact with human tissue	Titanium Epoxy resin Silicone rubber set plugs
Power source	Lithium carbon monoflouride battery
Storage temperature	20°C (68°F) to 25°C (77°F)

The EndoStim Implantable Bipolar Lead is a sterile, single-use device. The leads use stitch electrodes made of platinum-iridium wire, conductor coils and connector components made of stainless steel, and implantable-grade, biocompatible silicone for lead insulation. These materials are widely used for the construction of commercially available cardiac and gastric stimulation leads. Commercially-available implantable sutures exit through the electrode lumen and are attached to stainless steel surgical needles (the needles are removed during the implant procedure). The connection end of the lead is a standard IS-1 bipolar connector. The lead delivers stimulation pulses to the tissue through stitch electrodes at the distal end. During implantation, the stitch electrodes of the leads are sutured into the lower esophagus and secured into place.

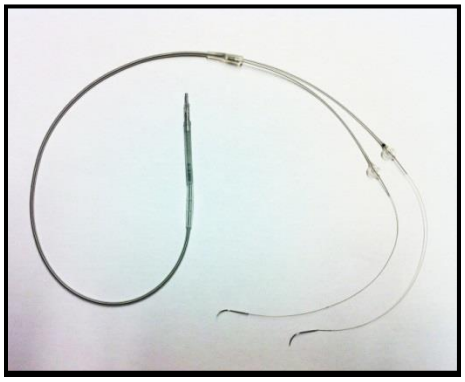

Figure 2. EndoStim Implantable Bipolar Lead

Main Implantable Bipolar Lead device specifications are provided in Table 2.

Table 2. EndoStim Implantable Bipolar Leads – Specifications

Lead	**Specification**
Connector	IS-1 BI
Mass	~4 g
Total Lead Length	45 cm from IS-1-B1 connector to end of electrodes
Bipolar Segment Length	35 cm
Monopolar Segment Lengths	10 cm (both)
Electrode Length	10 mm
Suture Length	5.5 cm
Suture Needle	Ski 19 mm, stainless steel
Electrodes	Platinum-iridium
Conductors	Cobalt/nickel (MP35N)
Sheathing	Silicone rubber
Suture	Nylon
Storage temperature	20°C (68°F) to 25°C (77°F)

The external Programmer System has two components: a Tablet PC with programmer software and a hand-held wand that contains communications electronics (Figure 3). The Tablet PC is provided by EndoStim and is pre-loaded with an embedded Windows OS and programmer software. The Tablet PC is intended only for use with the EndoStim system and features not essential for programming have been locked out.

Figure 3. Tablet PC with EndoStim Programmer Software and USB Programmer Wand

Main Programmer System specifications are provided in Table 3.

Table 3. EndoStim USB Programmer Wand - Specifications

Description	Specification
Height	140 mm
Width	62.7 mm
Thickness	30.5 mm
Mass	251 g
Storage temperature	5°C (41°F) to 37°C (99°F)

The IPG and Leads are intended to be implanted within the subject's body using conventional laparoscopy and remain in the body long term. The external Programmer System is intended to be used by medical personnel and/or a company technical representative in a clinical setting to retrieve IPG statistics and program the IPG.

Each investigator will be provided with an EndoStim Clinician Manual that provides instructions for use, warnings, precautions, etc. Devices used in this study will be labeled with "Caution: Investigational Device. Limited by United States law to investigational use." Device Accountability Logs will be used to track receipt and disposition of all investigational devices.

5. CLINICAL INVESTIGATION DESIGN

5.1 Purpose

The purpose of this investigation is 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).

5.2 Investigation Type

This investigation is a multicenter, randomized, double-blind, sham-controlled clinical investigation consisting of screening and baseline visits, followed by system implantation, and randomization (Treatment or Control Group). Randomized subjects complete a 6-month double-blind phase. At the 6-month visit, all subjects are moved to the treatment arm, Control Group subjects begin receiving electrical stimulation therapy, and all subjects are followed for an additional open-label treatment phase (Treatment Group subjects undergo electrical stimulation for an additional 6 months and Control Group subjects undergo electrical stimulation for 12 months, resulting in at least total 12 months of electrical stimulation therapy in both groups). Subjects continue on stimulation treatment and an extended open-label follow-up phase includes an 18-month post-stimulation phone interview followed by annual visits through 5 years. Figure 4 illustrates study-required visits and phases.

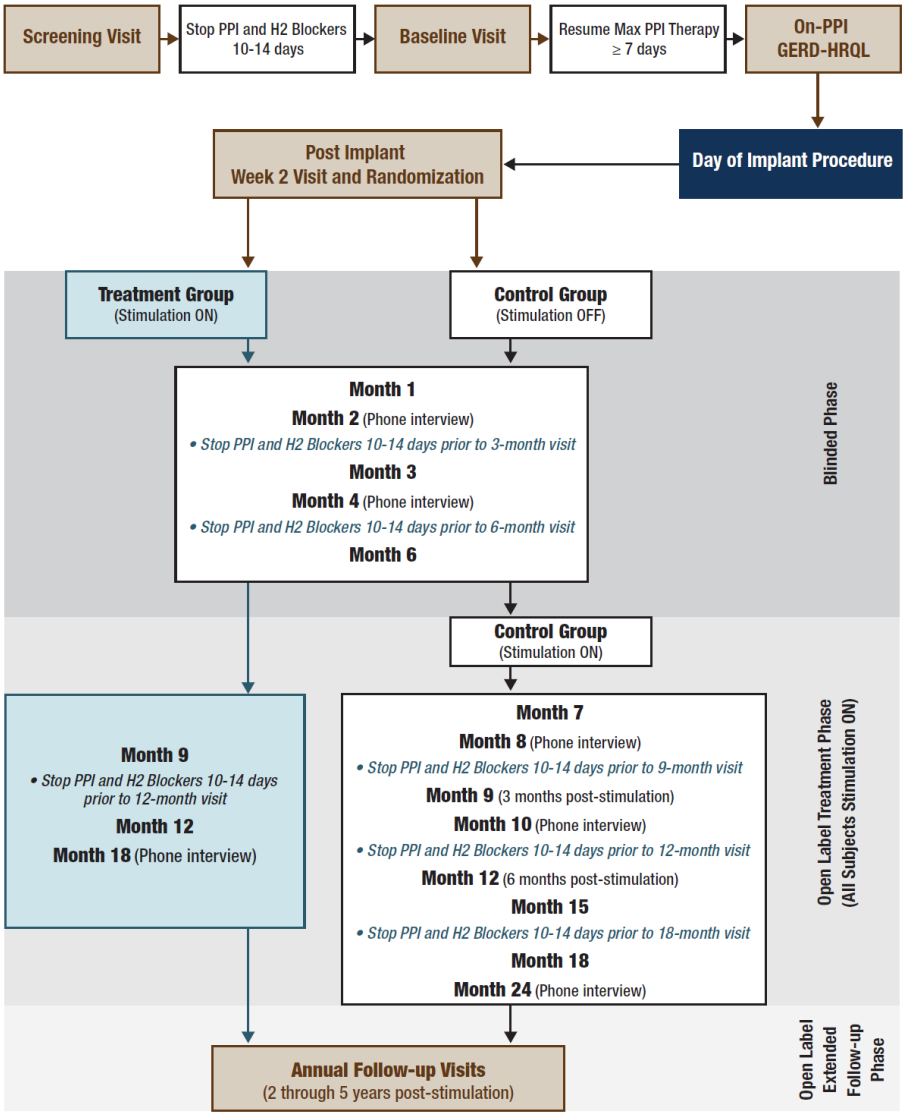

Figure 4. Study Visit Requirements and Phases

5.3 Investigational Site Scope

This investigation will be conducted at a maximum of 30 investigational sites globally with no more than 30% of enrolled subjects from sites located outside the United States.

5.4 Primary Safety Endpoint

The primary safety endpoint will be the rate of occurrence of device- and/ or procedure-related serious adverse events at the 12-month follow-up visit as adjudicated by the Clinical Events Committee.

5.5 Primary Efficacy Endpoint

Comparison between the treatment and control group, percentage (%) of subjects achieving pH success defined as normalization (pH < 4 for no more than 5.3% of monitoring time) or ≥ 50% improvement in their distal esophageal acid exposure at six months compared to their baseline distal esophageal pH both performed after at least 5 days off proton pump

inhibitors (PPIs) and at least 2 days off histamine 2 receptor antagonists (H2 blockers). Minimum 18 hours of esophageal pH recording will be considered adequate for all pH analysis.

Secondary Efficacy 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 electrical stimulation therapy follow-up visit (12-month visit for treatment group and 18-month visit for the control group) compared to their baseline **off-PPI and H2** blocker GERD-HRQL score.

5.5.1 Secondary EndpointsBlinded Phase (comparison between Treatment and Control Groups)

Secondary Endpoints will be taken from Blinded Phase where the comparison is between the Treatment Group and Control Group at the 6-month follow-up visit. Secondary Endpoints include the following comparisons:

a. 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 proton pump inhibitors (PPIs) and at least 2 days off histamine 2 receptor antagonists (H2 blockers).
b. Heartburn symptom frequency (day and night) and highest level of severity as measured by Subject Diary
c. Mean acid-suppression (PPI and H2 blocker) medication use
d. Regurgitation symptom frequency (day and night) and highest level of severity as measured by Subject Diary
e. Mean quality of life as measured by SF-12 scores

Open-Label Treatment Phase
Secondary Endpoints will be taken from the Open-Label Treatment Phase where the comparison is between baseline data and after 12 months of stimulation where each subject serves as its own control. Secondary Endpoints include:

a. Mean percentage (%) of time distal esophageal pH is <4.0
b. Number of subjects reporting 50% or more reduction in highest level of severity of heartburn symptoms as measured by daily Subject Diary
c. Number of subjects reporting 50% or more reduction in highest level of severity of regurgitation symptoms as measured by daily Subject Diary
d. Number of subjects able to stop regular use of acid-suppression medication (defined as 50% or more Subject Diary days without PPI use)
e. Number of subjects able to stop all use of acid-suppression medication (defined as 100% Subject Diary days without PPI use)
f. Number of subjects reporting 50% or more reduction in nocturnal symptoms of heartburn as measured by daily Subject Diary
g. Number of subjects reporting 50% or more reduction in nocturnal symptoms of regurgitation as measured by daily Subject Diary
h. 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. The baseline **on-PPI** score for comparison will be the score from the initial **on-PPI** GERD-HRQL, which was completed by the subject at the Screening visit.

i. Mean quality of life as measured by SF-12 scores

Other Endpoints of Interest

Blinded Phase

Other endpoints will be evaluated from the Blinded Phase where the comparison is between the Treatment Group and Control Group at the 6-month follow-up visit. Endpoints include:

a. Mean percentage (%) of time distal supine esophageal pH is <4.0
b. Percentage (%) of subjects achieving supine pH success defined as normalization (pH<4 for no more than 1.4% of supine period) or ≥50% improvement in their supine distal esophageal acid exposure compared to their baseline **off PPI/H2** blocker supine distal esophageal pH
c. Mean composite GERD-HRQL scores and responses to individual questions GERD-HRQL questionnaire (**off-PPI or H2**)
d. Sleep-related quality of life as measured by the Pittsburgh Sleep Quality Index (PSQI) scores
e. Bravo Esophageal pH Monitoring parameter characterization
f. Evaluation of the extent of mucosal injury from reflux as measured by endoscopy using the LA classification

Open-Label Treatment Phase

Other endpoints will be evaluated from the Open-Label Treatment Phase where the comparison is between baseline data and after 12 months of stimulation where each subject serves as its own control. Endpoints include:

a. Number of subjects achieving pH success defined as normalization of pH (pH < 4 for no more than 5.3% of monitoring time) or $\geq$50% improvement in their distal esophageal acid exposure compared to their baseline **off-PPI or H2** blocker distal esophageal pH
b. Number of subjects achieving supine pH success defined as normalization (pH < 4 for no more than 1.4% of supine period) or $\geq$50% improvement in their

supine distal esophageal acid exposure compared to their baseline **off-PPI or H2** blocker supine distal esophageal pH

c. Number of subjects reporting 50% or more improvement in sleep-related quality of life as measured by the Pittsburgh Sleep Quality Index (PSQI)
d. Rate and type of adverse events
e. Evaluation of the extent of mucosal injury from reflux as measured by endoscopy using the LA classification
f. Bravo Esophageal pH Monitoring parameter characterization
g. Mean composite GERD-HRQL scores and responses to individual questions GERD-HRQL questionnaire (**off-PPI or H2**)
h. Number of diary days with heartburn and their severity as measured by Subject Diary
i. Number of diary days with regurgitation and their severity as measured by Subject Diary
j. Sleep-related quality of life as measured by the Pittsburgh Sleep Quality Index (PSQI)
k. GERD symptoms as assessed by the Structured GI questionnaire
l. Work productivity impairment as measured by the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)
m. LES mean pressure (LES-MP) and end expiratory pressure (LES-EEP) as measured by high resolution manometry (HRM)
n. Characterize laryngopharyngeal reflux (LPR) symptoms as measured by the Reflux Symptom Index (RSI)
o. Assess change in body mass index (BMI)
p. Characterize healthcare resource utilization

Open-Label Extended Follow-Up Phase

Other endpoints will be evaluated from the Open-Label Extended Follow-Up Phase where the comparison is between baseline data and after 18 months of stimulation and at annual visits where each subject serves as its own control. Endpoints include:

a. Rate and type of adverse events
b. Mean composite GERD-HRQL scores and responses to individual questions on GERD-HRQL questionnaire (**off-PPI or H2**)
c. Number of diary days with heartburn and their severity as measured by Subject Diary
d. Number of diary days with regurgitation and their severity as measured by Subject Diary
e. Sleep-related quality of life as measured by the Pittsburgh Sleep Quality Index (PSQI)
f. GI symptoms as assessed by the Structured GI questionnaire
g. Work productivity impairment as measured by the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)
h. Mean quality of life as measured by SF-12 scores
i. Characterize laryngopharyngeal reflux (LPR) symptoms as measured by the Reflux Symptom Index (RSI)

j. Assess change in body mass index (BMI)
k. Characterize healthcare resource utilization

5.5.2 Subject Population

5.8.1 Inclusion Criteria

Subjects must meet all of the following study inclusion criteria:

a. Subject must be able and willing to provide written informed consent
b. Subject must be able and willing to comply with required study procedures and follow-up schedule
c. Subject is 22 – 75 years of age at the time of informed consent
d. 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 anti-reflux drug therapy, who continue to have symptoms despite maximum medical therapy or are "intolerant" - severe side-effects (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 listed in Table 4.
e. Subjects with symptomatic improvement on PPI therapy demonstrated by a composite GERD-HRQL score of ≥20 **off PPI**, and a ≥10-point improvement **on PPI** compared to the **off PPI** composite GERD-HRQL score. The **on-PPI** score to satisfy this criterion will be the score from the GERD-HRQL assessment completed after resuming PPIs following the Baseline visit. Patients who meet the definition above of PPI intolerant are not required to have ≥10-point improvement and are not required to take the GERD-HRQL for inclusion.
f. 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 PPIs** and at least 2 days **off H2** blockers. At least 18 hour of esophageal pH recording will be considered adequate and inclusion will be based on the day (at least 18 hours of valid data) with the highest acid exposure percentage time.
g. Subject has esophagitis ≤ Grade B (LA classification) as measured by upper endoscopy **off PPI and H2** blockers for 10-14 days
h. Subject has esophageal body contraction amplitude ≥ 30 mmHg for ≥ 30% of swallows and ≥ 30% peristaltic contractions on HRM or ≥ 30% peristaltic contractions with DCI >450.
i. Subject is a suitable surgical candidate able to undergo general anesthesia and laparoscopic surgery

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 non-GERD esophageal motility disorders that in the opinion of investigator precludes an anti-reflux 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/m^2
p. Subject has any significant multisystem diseases
q. Subject has an autoimmune or a connective tissue disorder (scleroderma, dermatomyositis, Calcinosis-Raynaud's-Esophagus 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 child-bearing 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, other than basal cell carcinoma, 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

5.6 Number of Subjects Required

To satisfy enrollment for the primary objectives, it is estimated a minimum of approximately 400 subjects will need to be consented to result in 120 subjects implanted and followed through the blinded and open-label treatment phases of the study. Maximum 1000 patients may be needed to enroll the maximum 200 patients if needed.

There are no minimum requirements for enrollments per site. In order to prevent a site from enrolling a majority of the subjects for the primary objectives, the maximum number of successfully implanted subjects at a single center will be approximately 25.

5.7 Investigation Duration

To satisfy enrollment for the primary objectives, the enrollment period is expected to be approximately 12 months followed by a 6-month, blinded phase and additional open-label treatment phase (an additional 6 months of follow-up for Treatment Group subjects and 12 months of follow-up for Control Group subjects) for primary and key secondary endpoint analysis. Additionally, the open-label extended follow-up phase will follow subjects out to 5 years. Thus, the expected duration of participation for each subject is approximately 5 years. However, study subjects will be followed until approval is granted from the U. S. Food and Drug Administration (FDA) or an official study closure is issued (when regulatory requirements have been satisfied per the protocol or a decision by EndoStim and/or regulatory authority).

5.8 Minimizing Bias

Potential sources of bias may include information bias (differential misclassification of subjective variables) and confounding bias (including treatment bias, where the practice of medicine differs by center). To minimize potential bias, the following measures have been incorporated:

- Study design incorporates subject randomization as well as subject and physician blinding.
- Classification rules are defined and all adverse events will be reviewed by the Clinical Events Committee, which is a group of independent physicians who are experts in the field and are not participating in the study as clinical investigators.
- Subject demographics will be assessed by collecting information on possible differences that may affect the study outcome. Information will be gathered on the subject's relevant medical background, diagnosis, concomitant medication use, etc.
- All centers will be required to follow the same versions of the protocol. There may be timing differences in submissions/approvals across sites.
- All investigators are required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators, to minimize bias due to financial interest in the outcome of the study.

In summary, potential sources of bias that may be encountered in this clinical investigation have been considered and minimized by careful study design.

5.9 Randomization Procedures

Within each investigational site, subjects will be block randomized to either treatment (stimulation on) or control group (stimulation off) in a 1:1 ratio. Block sizes will be randomly varied between 2 and 4 to ensure non-predictability of other subjects' assignments by the physician and subject when the scheduled unblinding occurs during the 6-month visit. The randomization assignments will be generated in advance of the start of the trial by the unblinded statistician and entered into the electronic database's randomization assignment module. At the time of randomization, the unblinded site technician will request and receive the randomization assignment from the system. Both subject and physician will remain blinded to this assignment.

5.10 Protocol-Required Testing

Protocol-required testing at a given visit interval may be completed on separate dates from the office visit if required by the institution as long as the testing is performed in compliance with protocol requirements and occurs within the corresponding visit window.

In the event there are technical issues with a protocol-required test precluding accurate and/or complete data collection, the test may be repeated one time. Both the initial test and/or assessment and the repeat test and/or assessment will be reported on the CRF. The repeat test and/or assessment will be reported as an Unscheduled visit.

5.11 Off-PPI and H2 Blocker Evaluation Periods

This protocol specifies certain time periods in which subjects are asked to be off proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2 blockers) for 10 – 14 days. Recommended minimum **off PPI and H2** blocker evaluation periods for specific study-required elements are as follows:

- ≥ 5 days **off PPI** and ≥ 2 days **off H2** blockers prior to Bravo Esophageal pH monitoring
- ≥ 10 days **off PPI and H2** blockers prior to completion of "off-PPI/H2 blocker" questionnaires
- ≥ 10 days **off PPI and H2** blockers prior to endoscopy for evaluation of esophagitis

5.12 Guidelines for Acid-Suppressive or Acid-Neutralizing Medication Use

Before implantation of an investigational device, it is important that the patient has received maximum medical therapy. PPI dosages above the FDA-approved dosage (e.g. double-dose or BID dosing) may be appropriate in select cases. However, little data exist substantiating either the safety or efficacy of these higher doses, and ACG guidelines report only a low level of evidence to support these dosages. Additionally, there is increasing concern about PPI-related adverse events, some of which appear to be dose-related. Finally, level one evidence demonstrates that switching from one brand of PPI to another at QD dosing is as effective as BID dosing of the PPI. For these reasons, for purposes of this trial, maximum medical therapy is to be defined as QD dosage of a PPI (healing dosage) for a minimum of three months **and** use of either BID dosage of PPIs **or** use of a different PPI for at least one additional month (at healing dosage). Patients' self-report of medication

history satisfying these criteria to the site PI will be considered appropriate documentation for this issue.

Table 4 below provides the dosages that will be acceptable in order to meet the definition above for maximum medical therapy.

Table 4. Acceptable PPI Dosages for study inclusion

Medication	Maximal FDA Approved Healing Dosage* (per day)
Omeprazole (Prilosec)	20mg
Lansoprazole (Prevacid)	30mg
Pantoprazole (Protonix)	40mg
Rabeprazole (Aciphex)	20mg
Esomeprazole (Nexium)	20mg or 40mg
Dexlansoprazole (Dexilant)	60mg

* Proton Pump Inhibitors: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults, FDA/CMS publication Oct 2015.

During **off-PPI and H2** blocker intervals, antacid use is allowed for symptom relief and recorded in the Subject Diary. Subjects unable to comply during **off PPI and H2** blocker intervals will be allowed to immediately resume use of these medications and will continue to be followed. However, pH testing will not be performed in cases where a subject cannot tolerate cessation of these medications for the minimum required period and the data will be managed as missing data according to the protocol.

During intervals in which the subject may take PPIs and H2 blocker medications, it is recommended that the subject take these medications only when needed to control GERD symptoms. Recommendations for diet and life style changes for subjects with GERD will be provided to the subject at every visit (Appendix B).

Antacid use will be allowed for breakthrough symptoms and should be prescribed to the subjects by the PI:

- Subjects will be allowed Gelusil® or Gaviscon® antacid according to the package labeling (acid-suppressive and neutralizing medications and the indication for which these medications are taken will be recorded on the Medications CRF).

For subjects with suboptimal control of GERD symptoms following device implant and randomization despite antacid therapy for at least 2 weeks, rescue anti-reflux medications will be initiated immediately using the following treatment regimen:

- H2 blockers: famotidine (Pepcid or Pepcid Complete Chewable) 10 mg or ranitidine (Zantac) 150 mg, 1-2 tablets once to twice daily, with or without antacids as needed
- If the subject has an inadequate response to at least 2 weeks of H2 blockers, they may proceed to omeprazole (Prilosec/Losec) or esomeprazole (Nexium) 20 mg or 40mg once or twice daily with or without antacid or H2 blockers.

  Based on the severity of symptoms, as determined by the PI, subjects with breakthrough symptoms may immediately be prescribed Nexium/Prilosec in lieu of antacids and H2 blockers.

Subjects diagnosed via endoscopy with Grade C or D esophagitis during the study will be treated with the same baseline dose and brand of PPI that had previously been proven to heal the esophagitis in that particular patient. Patients will undergo a repeat endoscopy at their 12 month visit and those with persistent Grade C or D esophagitis will be exited from the study.

5.13 Subject Diary and Questionnaire Administration and Review

Paper diaries and questionnaires will be completed by the subject and entered into the electronic CRF by site personnel.

For the Subject Diary, a minimum of 10 days of daily diary completion is required prior to the office visit and must occur outside of the required **off PPI and H2** blocker evaluation period. This data will be used for the endpoint evaluation of medication use. Additionally, subjects will continue to complete the daily diary during the required **off-PPI and H2** blocker evaluation period of 10-14 days prior to the office visit; however, this data will not be included in the endpoint evaluation of medication use.

The severity of the worst episode will be assessed as measured by Subject Diary averaged over the most recent 14 days with no symptoms equal to 0, mild symptoms equal to 1, moderate equal to 2, and severe equal to 3. In addition, days (nights) with heartburn will be calculated as the percent of the 14 days (nights) with any regurgitation symptoms. The severity of the worst heartburn episode, will also be assessed as measured by Subject Diary using the same calculations as for regurgitation.

5.14 Methodology for Maintenance of Blinding

Only a non-blinded technician will have access to device setting information at each site. (Note that randomization assignments are protected by the use of a special password with the EndoStim programmer). Additionally, all subjects will undergo the same test protocols and device setting sessions during the blinded phase of the study. At the beginning of the 1-month and 6-month visits, subjects will be asked to identify to which treatment group they believe they have been assigned. This information will be documented in the medical record and submitted to EndoStim via a CRF.

In the event of an emergency, the site may place a magnet over the location of the IPG implant to temporarily suspend therapy (per the EndoStim Clinician Manual) and contact EndoStim for further instructions.

6. TESTS AND PROCEDURES

Clinical data will be collected at the time of screening, enrollment, implant, follow-up visits, and unscheduled visits. Data collection will include, but not be limited to, system parameter modifications, subject symptom and diagnostic data, new or worsening adverse events, study deviations and study completion or discontinuation. Data will be collected via electronic CRFs, subject daily diaries, and subject questionnaires. Data collection requirements are summarized in the tables that follow.

Table 5. Schedule of Events: Screening, Baseline, and Implant Procedure, Treatment and Control Groups

Visit Interval	Screening Visit (On PPI and/or H2 Blockers)			Baseline Visit (Off PPI/H2 Blockers)		GERD-HRQL for inclusion[2]	Implant Procedure
				Day 1	Day 3[1]		
Visit Window				At least 21 Days After Screening Visit	~48 Hours After Day 1 Visit	At least 7 days after resuming maximum PPI therapy (**on PPI**)	≤6 Months After Baseline Visit
Test or Procedure							
Subject Informed Consent	X	**Start Daily Subject Diary ≥ 10 Days Before Off PPI and H2 Blockers Period**	**Stop PPI and H2 Blockers 10-14 Days Before Baseline Visit** (antacid medication use allowed and recorded in Subject Diary)				
Inclusion/Exclusion	X			X		X	X
GERD-HRQL	X[3]			X		X	
Reflux Symptom Index (RSI)	X			X			
Medical History	X						
Physical Exam	X[4]			X[4]			X
Medication Review	X			X			X
Pittsburgh Sleep Quality Index (PSQI)	X			X			
WPAI Questionnaire	X			X			
Structured GI Symptoms Questionnaire	X			X			
SF-12 Questionnaire	X			X			
Healthcare Resource Utilization Quest.	X						
Diet & Lifestyle Instructions Review	X			X			X
Subject Diary Collection				X			
Endoscopy				X[5]			
Esophageal Manometry (HRM)	X[5]			X[5]	X[5]		
Bravo Esophageal pH Monitoring (48 hrs) Probe Insertion Results Review and Analysis				X[5]	 X		
12-Lead ECG Monitoring	X[6]			X[6]			X[6]
Complete Blood Count	X[6]			X[6]			X[6]
Chem7 or Basic Metabolic Panel	X[6]			X[6]			X[6]
HbA1c	X[6]			X[6]			X[6]
Urine Pregnancy Test	X[6]			X[6]			X[6]
System Implantation and ECG							X
Device Interrogation and Lead Impedance							X
Adverse Event Assessment	X			X	X		X

[1] An in-person Day 3 visit is optional. If no other procedures are planned at this visit, the patient may return the Bravo equipment, per the site's instructions. A brief phone visit should be conducted to confirm the equipment was returned and any adverse events reported should be documented.

[2] GERD-HRQL for inclusion is not required if the subject meets the protocol definition of PPI-intolerant

[3] This on-PPI GERD-HRQL assessment will not be used to assess inclusion criteria. This will be the **on-PPI** score that is used for baseline on-PPI comparisons. This Screening visit questionnaire should be completed by all subjects, even if the subject is PPI-intolerant and not taking PPIs.

[4] One physical exam is required prior to determining eligibility. May be done at Screening or Baseline visit.

[5] Assess availability and acceptability of prior data collection within the last 6 months (See Section 6.1). If prior data collection is not used, one test required prior to implant

[6] One test required prior to implant, may be completed during screening, baseline or day of procedure (prior to the procedure) per institution preference

Table 6. Schedule of Events Post-Implant Procedure: Blinded Phase, Treatment and Control Groups

Visit Interval	**Post Implant Week 2 and Randomization**	**Month 1**	**Phone Interview Month 2** ☎			**Month 3**		**Phone Interview Month 4** ☎			**Month 6**	
						Day 1	**Day 3**[1]				**Day 1**	**Day 3**[1]
Visit Window *(Relative to Date of Implant)*	7-14 Days After Implant Procedure	+/-14 Days	+/-14 Days			+/-14 Days	~48 Hours	+/-14 Days			+/-21 Days	~48 Hours
Test or Procedure												
Physical Exam		X				X					X	
GERD-HRQL	X	X	X			X		X			X	
Reflux Symptom Index (RSI)		X	X			X		X			X	
Medication Review	X	X	X			X		X			X	
Adverse Event Assessment	X	X	X			X	X	X			X	X
Diet & Lifestyle Instructions Review	X	X				X					X	
Subject Diary Collection						X					X	
Device Interrogation and Impedance Device Parameter Optimization	X	X				X[2]	X[2] X				X[2]	X[2] X
Bravo Esophageal pH Monitoring (48 hrs) Probe Insertion Results Review and Analysis						X	 X				X	 X
Urine pregnancy Test						X					X	
Endoscopy						X[3]					X	
Esophageal Manometry (HRM)											X[4]	X[4]
Complete Blood Count											X	
Chem7 or Basic Metabolic Panel											X	
HbA1c											X	
Pittsburgh Sleep Quality Index (PSQI)											X	
WPAI Questionnaire											X	
Structured GI Symptoms Questionnaire											X	
SF-12 Questionnaire											X	
Healthcare Resource Utilization Quest											X	
Randomization	X											
Turn Stimulation On	Treatment Group Only											Control Group Only

Start Daily Subject Diary ≥ 10 Days Before Off PPI and H2 Blockers Period

Stop PPI and H2 Blockers 10-14 Days Before 3-Month Visit

(antacid medication use allowed and recorded in Subject Diary)

Start Daily Subject Diary ≥ 10 Days Before Off PPI and H2 Blockers Period

Stop PPI and H2 Blockers 10-14 Days Before 6-Month Visit

(antacid medication use allowed and recorded in Subject Diary)

[1] An in-person Day 3 visit is optional. Sites may elect to have the patient return the Bravo equipment via shipment per the site's instructions. If the patient does not return to the clinic for this visit, a brief phone visit should be conducted to confirm the equipment was returned and any adverse events reported should be documented. The patient would need to return to the clinic after the pH results are available only if those results qualify the patient for device parameter optimization.

[2] For two-day visits, device interrogation and lead impedance can be done on either day; it is not required on both days.

[3] An endoscopy may be performed to aid in the placement of the Bravo capsule.

[4] Manometry may be done at the Day 1 or Day 3 visit.

Table 7. Schedule of Events Post-Implant Procedure: Open-Label Treatment Phase, Treatment Group

Visit Interval	**If pH testing is not planned for 9-Month visit: Start Daily Subject Diary ≥ 10 Days Before Visit** **If pH testing is planned: Start Diary ≥ 10 Days Before Off PPI and H2 Blockers Period**	**Only if pH testing is planned: Stop PPI and H2 Blockers 10-14 Days Before 9-Month Visit**	**Month 9**	**Start Daily Subject Diary ≥ 10 Days Before Off PPI and H2 Blockers Period**	**Stop PPI and H2 Blockers 10-14 Days Before 12-Month Visit** (antacid medication use allowed and recorded in Subject Diary)	**Month 12**		**Phone Interview Month 18 ☎**
						Day 1	**Day 3[1]**	
Visit Window *(Relative to Date of Implant)*			+/-30 Days			+/-30 Days	~48 Hours	+/-30 Days
Test or Procedure								
Physical Exam			X			X		
GERD-HRQL			X			X		X
Reflux Symptom Index (RSI)			X			X		X
Medication Review			X			X		X
Adverse Event Assessment			X			X	X	X
Diet & Lifestyle Instructions Review			X			X		
Subject Diary Collection			X			X		
Device Interrogation and Impedance Device Parameter Optimization			X			X[2]	X[2] X	
Bravo Esophageal pH Monitoring (48 hrs) Probe Insertion Results Review and Analysis			X[3]			X	 X	
Urine pregnancy test			X			X		
Endoscopy			X[3]			X[4]		
Complete Blood Count						X		
Chem7 or Basic Metabolic Panel						X		
HbA1c						X		
Pittsburgh Sleep Quality Index (PSQI)						X		
WPAI Questionnaire						X		
Structured GI Symptoms Questionnaire						X		
SF-12 Questionnaire						X		
Healthcare Resource Utilization Quest.						X		

[1] An in-person Day 3 visit is optional. Sites may elect to have the patient return the Bravo equipment via shipment per the site's instructions. If the patient does not return to the clinic for this visit, a brief phone visit should be conducted to confirm the equipment was returned and any adverse events reported should be documented. The patient would need to return to the clinic after the pH results are available only if those results qualify the patient for device parameter optimization.

[2] For two-day visits, device interrogation and lead impedance can be done on either day; it is not required on both days.

[3] pH monitoring is optional per investigator discretion based on subject symptoms. An endoscopy may be used to aid in placement of the Bravo capsule. A Day 3 visit would be optional per the footnote above.

[4] A diagnostic endoscopy is required at 12 months only if esophagitis was present at the 6-month visit. An endoscopy may be used to aid in the placement of the Bravo capsule.

Table 8. Schedule of Events Post-Implant Procedure: Open-Label Treatment Phase, Control Group

Visit Interval	**Month 7** (month 1 of stimulation)	**Phone Interview Month 8** ☎	**Start Daily Subject Diary ≥ 10 Days Before Off PPI and H2 Blockers Period**	**Stop PPI and H2 Blockers 10-14 Days Before 9-Month Visit** (antacid medication use allowed and recorded in Subject Diary)	**Month 9** (month 3 of stimulation)		**Phone Interview Month 10** ☎	**Start Daily Subject Diary ≥ 10 Days Before Off PPI and H2 Blockers Period**	**Stop PPI and H2 Blockers 10-14 Days Before 12-Month Visit** (antacid medication use allowed and recorded in Subject Diary)	**Month 12** (month 6 of stimulation)	
					Day 1	**Day 3[1]**				**Day 1**	**Day 3[1]**
Visit Window *(Relative to Date of Implant)*	+/-14 Days	+/-14 Days			+/-14 Days	~48 Hours	+/-14 Days			+/-21 Days	~48 Hours
Test or Procedure											
Physical Exam	X				X					X	
GERD-HRQL	X	X			X		X			X	
Reflux Symptom Index (RSI)	X	X			X		X			X	
Medication Review	X	X			X		X			X	
Adverse Event Assessment	X	X			X	X	X			X	X
Diet & Lifestyle Instructions Review	X				X					X	
Subject Diary Collection					X					X	
Device Interrogation and Lead Impedance Device Parameter Optimization	X				X[2]	X[2] X				X[2]	X[2] X
Bravo Esophageal pH Monitoring (48 hours) Probe Insertion Results Review and Analysis					X[3]	 X				X	 X
Urine pregnancy Test					X					X	
Endoscopy					X[3]					X[4]	
Esophageal Manometry (HRM)										X[5]	X[5]
Complete Blood Count, Chem panel, HbA1c										X	
PSQI, WPAI, Structured GI, SF-12, and Healthcare Resource Utilization Quest.										X	

[1] An in-person Day 3 visit is optional. Sites may elect to have the patient return the Bravo equipment via shipment per the site's instructions. If the patient does not return to the clinic for this visit, a brief phone visit should be conducted to confirm the equipment was returned and any adverse events reported should be documented. The patient would need to return to the clinic after the pH results are available only if those results qualify the patient for device parameter optimization.

[2] For two-day visits, device interrogation and lead impedance can be done on either day; it is not required on both days.

[3] pH monitoring is optional per investigator discretion based on subject symptoms. An endoscopy may be performed to aid in the placement of the Bravo capsule. A Day 3 visit would be option per the footnote above.

[4] A diagnostic endoscopy is only required in subjects who had esophagitis at their 6-month visit. An endoscopy may be performed to aid in the placement of the Bravo capsule.

[5] Manometry may be done at the Day 1 or Day 3 visit.

Table 9. Schedule of Events Post-Implant Procedure: Open-Label Treatment Phase, Control Group Continued

Visit Interval	**If pH testing is not planned for 15-Month visit: Start Daily Subject Diary ≥ 10 Days Before Visit** **If pH testing is planned: Start Diary ≥ 10 Days Before Off PPI and H2 Blockers Period**	**Only if pH testing is planned: Stop PPI and H2 Blockers 10-14 Days Before 15-Month Visit**	**Month 15** **(month 9 of stimulation)**	**Start Daily Subject Diary ≥ 10 Days Before Off PPI and H2 Blockers Period**	**Stop PPI and H2 Blockers 10-14 Days Before 18-Month Visit** (antacid medication use allowed and recorded in Subject Diary)	**Month18 (month 12 of stimulation)**		**Phone Interview Month 24 (month 18 of stimulation)** ☎
						Day 1	**Day 3[1]**	
Visit Window *(Relative to Date of Implant)*			+/-30 Days			+/-30 Days	~48 Hours	+/-30 Days
Test or Procedure								
Physical Exam			X			X		
GERD-HRQL			X			X		X
Reflux Symptom Index (RSI)			X			X		X
Medication Review			X			X		X
Adverse Event Assessment			X			X	X	X
Diet & Lifestyle Instructions Review			X			X		
Subject Diary Collection			X			X		
Device Interrogation and Impedance Device Parameter Optimization			X			X	X[2] X	
Bravo Esophageal pH Monitoring Probe Insertion Results Review and Analysis			X[3] X[1]			X	 X	
Urine pregnancy Test			X			X		
Endoscopy			X[4]			X[5]		
Complete Blood Count, Chem panel, HbA1c						X		
PSQI, WPAI, Structured GI, SF-12 and Healthcare Resource Utilization Quest.						X		

[1] An in-person Day 3 visit is optional. Sites may elect to have the patient return the Bravo equipment via shipment per the site's instructions. If the patient does not return to the clinic for this visit, a brief phone visit should be conducted to confirm the equipment was returned and any adverse events reported should be documented. The patient would need to return to the clinic after the pH results are available only if those results qualify the patient for device parameter optimization.

[2] For two-day visits, device interrogation and lead impedance can be done on either day; it is not required on both days.

[3] pH monitoring is optional per investigator discretion based on subject symptoms. An endoscopy may be performed to aid in the placement of the Bravo capsule. A Day 3 visit would be option per the footnote above.

[4] An endoscopy may be performed to aid in the placement of the Bravo capsule

[5] A diagnostic endoscopy is only required in subjects who had esophagitis at their 12-month visit. An endoscopy may be used to aid in the placement of the Bravo capsule.

Table 10. Schedule of Events Post-Implant Procedure: Open-Label Extended Follow-Up Phase

Visit Interval **Visit Window** *(Relative to the Date of Stimulation Turn On)* **Test or Procedure**	**Start Daily Subject Diary ≥ 10 Days Before Annual Visit**	**Annual Follow-Up Visits Years 2 to 5** +/-30 Days
Physical Exam		X
GERD-HRQL		X
Reflux Symptom Index (RSI)		X
Medication Review		X
Adverse Event Assessment		X
Diet & Lifestyle Instructions Review		X
Subject Diary Collection		X
Device Interrogation and Lead Impedance		X
Device Parameter Optimization		X
Urine pregnancy test		X
Pittsburgh Sleep Quality Index (PSQI)		X
WPAI Questionnaire		X
Structured GI Symptoms Questionnaire		X
SF-12 Questionnaire		X
Healthcare Resource Utilization Questionnaire		X

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5.24 Screening Visit

Potential subjects will be identified by participating investigators and study personnel. After a potential study participant has been pre-screened to assure that they satisfy some of the basic inclusion/exclusion criteria of the study, and prior to initiation of any study-specific procedures, the clinical investigator will obtain informed consent. The process of obtaining informed consent shall avoid any coercion of, or undue influence of, subjects to participate, not waive or appear to waive subject's legal rights, use language that is non-technical and understandable to the subject, provide ample time for the subject to consider participation, and include personally dated signatures of the subject and of the clinical investigator acknowledging that participation in the study is voluntary. The clinical investigator will provide the Informed Consent form to the subject in a language that he or she is able to read and understand. In the event the subject cannot read and/or write, witnessed informed consent will be allowed. The clinical investigator will document on the Screening CRF that the informed consent, including data privacy authorization, has been obtained by recording the date the subject signed the Informed Consent. The clinical investigator will file the signed Informed Consent in the hospital/clinic chart or with the study subject documentation. A copy of the fully executed Informed Consent shall be given to the subject.

The signed Informed Consent form must be available for review by the designated EndoStim monitor prior to completing monitoring of subject-related data. An Informed Consent template is located in Appendix A. Any changes to this Informed Consent template must be approved by EndoStim and the IRB reviewing the application before any subject may be enrolled in the study.

The point of enrollment is when a subject and investigator have signed the Informed Consent form. A Screening Visit CRF must be completed for all enrolled subjects.

Screening Visit data collection will include demographics, medical history, vital signs, and physical examination. Medication use will also be recorded. All medications the subject is taking, and applicable clinical indication for each, are to be recorded on the Prior and Concomitant Medication CRF, including all acid suppressive and acid neutralizing medications. This includes over-the-counter as well as prescribed medications.

Esophageal HRM, endoscopy and Bravo pH testing are diagnostic procedures used in clinical practice for the evaluation of GERD. Subjects who have undergone these tests as standard of care within the prior 6 months with evaluable test reports may provide test

reports to the investigator for consideration of satisfying screening test requirements provided the subject's condition has been stable. The decision to include prior screening tests is at the discretion of the clinical investigator provided test methodology meets the following criteria:

- Testing must be completed using the same type of equipment planned for use at the follow-up visits
- Testing was done under requirements that meet the protocol (for example, Bravo pH testing performed after at least 5 days **off PPIs** and at least 2 days **off H2** blockers; endoscopy performed after at least 10 days **off PPIs and H2** blockers)
- Endoscopy and Bravo pH testing must have been performed by the PI or sub-investigator
- Only data from the first 48 hours of a prior Bravo pH test will be considered for this study. Any data collected beyond 48 hours will be disregarded.

If prior testing is accepted, the clinical investigator will review prior test reports to assess applicable subject inclusion/exclusion prior to moving the subject forward in the screening process.

Subjects meeting the study selection criteria will complete subject questionnaires (Appendix B) while **on PPIs and/or H2** blockers ("**on-PPI/H2** blocker questionnaires") to assess baseline GERD symptoms:

- Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) Heartburn Questionnaire. This **on-PPI** GERD-HRQL assessment will not be used to assess inclusion criteria. This will be the **on-PPI** score that is used for baseline comparisons for relevant endpoint evaluations.
- Reflux Symptom Index (RSI)
- Pittsburgh Sleep Quality Index (PSQI)
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI)
- Structured GI Symptoms (Structured GI)
- SF-12
- Healthcare resource utilization

Study procedure-related adverse events will be assessed. Diet and lifestyle instructions (Appendix B) will be provided and reviewed with the subject.

In preparation for Baseline Visit Day 1, the subject will be instructed in the use of the Subject Diary. Daily diary completion is required at a minimum of 10 days prior to the required o**ff PPI and H2** blocker evaluation period. Additionally, subjects will continue to complete the daily diary during the required **off PPI and H2** blocker evaluation period of 10-14 days prior to the next office visit. During this off-medication time period, antacid use for symptom relief is allowed and will be documented by the subject in the Subject Diary. The subject will be reminded to fast for approximately 8 hours prior to the Bravo probe placement on Baseline Visit Day 1.

5.25 Baseline Visit (Day 1)

All medications the subject is taking are to be recorded on the Prior and Concomitant Medication CRF, including antacids and antisecretory medication use. Compliance with **off-PPI/H2** blocker instructions will be confirmed (Section 5.15 and 5.16).

The GERD-HRQL questionnaire will be given to the subject for completion ("**off-PPI/H2** blocker questionnaire"). Sites may administer the GERD-HRQL over the phone prior to the in-person Baseline Visit, as long as the patient has been off PPIs for at least 10 days. In order to proceed in the study, subjects must have a Baseline Visit GERD-HRQL score ≥ 20 following at least 10-14 days **off-PPI** and at least 10 points higher than their **on-PPI** GERD-HRQL score that will be assessed after they return to maximum PPI therapy following the Baseline Visit (unless they are PPI-intolerant). Note that the **on-PPI** GERD-HRQL completed at the Screening visit should not be used for evaluating inclusion criteria. Subjects who do not meet these inclusion criteria will be exited from the study as a screen failure.

The Subject Diary will then be reviewed with the subject. Subject Diary completion compliance of approximately 80% of the diary days is required for the subject to continue in the study.

Additional subject questionnaires will be provided to the subject to assess baseline **off-PPI/H2** blocker GERD symptoms ("**off-PPI/H2** blocker questionnaires"):

- Reflux Symptom Index (RSI)
- Pittsburgh Sleep Quality Index (PSQI)
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI)
- Structured GI Symptoms
- SF-12

Subjects unable to tolerate withdrawal from PPIs or H2 blockers will not be included in the study.

If not performed within the last 6 months (per Section 6.1), esophageal HRM will be performed during the Baseline Visit on Day 1 or 3. Subjects must have esophageal body contraction amplitude ≥ 30 mmHg for ≥ 30% of swallows and ≥ 30% peristaltic contractions on HRM or ≥ 30% peristaltic contractions with DCI >450 to be included in this study. Subjects will be excluded from participation in this study if they have a non-GERD esophageal motility disorder that in the opinion of investigator precludes an anti-reflux procedure.

One of each of the following tests is required for the purpose of subject screening prior to the implant procedure. These tests may be completed on separate visits per site requirements (within the visit interval) or can instead be completed at the Screening Visit or on the day of implant (prior to the implant procedure) per site preference.

- Baseline laboratory tests (complete blood count, chemistry 7 panel or basic metabolic panel, and HbA1c)
- Baseline 12-lead electrocardiogram (ECG)
  - Any potential cardiac finding that could potentially preclude inclusion in the study should be ruled out via standard clinic practices prior to moving the subject forward in the screening process.
- Urine pregnancy test
  - Female subjects of child-bearing potential must be on a reliable form of birth control and undergo a urine pregnancy test. Note: Female subjects who are pregnant or nursing, or intend to become pregnant during the study period are excluded from study participation.

Subjects will also undergo an upper endoscopy. Subject must have either no appearance of esophagitis or esophagitis $\leq$ Grade B (LA classification) to be included in this study. Subject will be excluded from participation in this study if any of the following are found:

- Esophageal stricture or significant esophageal anatomic abnormalities (obstructive lesions, etc.)
- Barrett's esophagus or any grade of dysplasia
- Suspected or confirmed esophageal or gastric cancer
- Esophageal or gastric varices

Subjects will undergo endoscopic Bravo Esophageal pH probe placement at the end of the Baseline Visit Day 1. The subject will be asked to continue **off-PPI and H2** blockers and to return the Bravo equipment for analysis as instructed by the site.

Adverse events will be assessed. Diet and lifestyle instructions (Appendix B) will be provided and reviewed with the subject.

5.26 Baseline Visit (Day 3)

The subject will then return the Bravo equipment for analysis as instructed by the site. In order to proceed in the study, subjects must have exhibited excessive lower esophageal acid exposure defined as pH < 4 for $\geq$ 6.0% of total time, based on the day (at least 18 hours of valid data) with the highest acid exposure percentage time. Only pH data from the first 48 hours will be considered for this study. Any data collected beyond 48 hours will be disregarded. Subjects who do not meet this inclusion criterion will be excluded from the study as a screen failure.

Subjects who pass the pH criteria may then undergo esophageal HRM, if needed. Subjects must have esophageal body contraction amplitude $\geq$ 30 mmHg for $\geq$ 30% of swallows and $\geq$ 30% peristaltic contractions on HRM or ≥30% peristaltic contractions with DCI >450 to be included in this study. Subjects will be excluded from participation in this study if they have a non-GERD esophageal motility disorder that in the opinion of investigator precludes an anti-reflux procedure.

Adverse events will be assessed.

5.27 GERD-HRQL for Inclusion

After the Baseline visit, subjects should resume maximum PPI therapy for at least 7 days and then complete an **on-PPI** GERD-HRQL. This may be done in an additional clinic visit, in a phone visit with the study coordinator or the subject may complete the questionnaire at home and return it to the study coordinator as instructed by the site.

This **on-PPI** GERD-HRQL score will be used to determine study eligibility (i.e., this score must indicate at least a 10-point improvement from the patient's **off-PPI** score). This GERD-HRQL score will not be used as a baseline score for any endpoint evaluations. Note that subjects who meet the protocol definition of PPI intolerant (Inclusion Criterion 'd') are not required to take the GERD-HRQL for inclusion since they are unable to take PPI and also are not required to have the 10-point score differential.

GERD-HRQL question #9 regarding bloating is being added under this protocol amendment (see Appendix B). Question #9 will not be included in the score that is used to determine eligibility. Further details on the analysis of results from this question will be addressed in the statistical analysis plan.

Subjects may remain **on PPIs** until the Randomization visit.

5.28 Implant Procedure

On the day of the implant procedure, subjects will undergo a routine pre-operative physical examination and medication use review. Any change in the subject's health status since the prior visit should be noted. Subjects must be deemed a suitable surgical candidate able to undergo general anesthesia and laparoscopic surgery to proceed with the implant procedure.

The following baseline tests not performed during the Screening or Baseline Visit may be completed on the day of implant, prior to the implant procedure: 12-lead ECG monitoring and laboratory tests (complete blood count, chemistry 7 panel or basic metabolic panel, HbA1c).

Female subjects of child-bearing potential must be on a reliable form of birth control and undergo a baseline urine pregnancy test if not done during the Baseline Visit. Female subjects who are pregnant are excluded from study participation.

At this point, the investigator should confirm that the subject meets all evaluable selection criteria before proceeding to the implant procedure.

To begin the implant procedure, the subject will be anesthetized or sedated per standard laparoscopy practices. Standard laparoscopy will be performed using standard institutional protocol and sterile techniques. The EndoStim lead and stimulator will be implanted according to the clinician manual. A video recording of the implant procedure will be

performed where possible. The device will be interrogated and lead impedance assessed to ensure proper system placement and functioning.

Subjects who are unable to undergo a successful system implantation, for whatever reason, will continue to be monitored through the post-implant week 2 visit, but will not be randomized. Proceed to Section 11.5 regarding subject discontinuation.

Following recovery from the laparoscopic procedure, the subject will be monitored with an ECG for approximately 5 minutes of baseline, followed by approximately 30 minutes while the device is programmed initially with the nominal settings (see Table 11) and delivering stimulation therapy, and a final session of approximately 25 minutes while stimulation is off (total duration of approximately 60 minutes). Stimulation will remain off. Final device settings will be confirmed.

The subject will recover following standard institutional protocol and be discharged at the investigator's discretion. Symptoms of heartburn, chest pain or discomfort, and dysphagia or any other symptoms secondary to the device placement will be recorded. The subject should wear a compression binder over the pocket for at least 30 days post-operatively.

Subjects will be given the following post-EndoStim diet instructions:

- STAGE 1: CLEAR LIQUID DIET - Night of Surgery
- STAGE 2: SOFT DIET - Morning after surgery. Continue at this stage for 3-7 days after surgery or as tolerated
- STAGE 3: START TRANSITION TO REGULAR DIET - About 3-7 days after surgery
- STAGE 4: ACHIEVE REGULAR DIET - 3 to 6 weeks after surgery

Adverse events will be assessed and recorded. The subject will be released with instructions to continue their baseline PPI use as prescribed. Diet and lifestyle instructions (Appendix B) will be provided and reviewed with the subject.

5.29 Post-Implant Week 2 Visit and Randomization

At the post-implant week 2 follow-up visit, the incision sites will be evaluated and sutures removed as appropriate. The device will be interrogated and lead impedance will be checked to ensure proper functionality. If the system is unable to perform as intended, the subject may elect to the following as appropriate:

- Undergo laparoscopy to reposition or replace the lead
- Explant the device and/or lead (Section 6.12)
- Replace the device and/or lead (Section 6.13)

All medications the subject is taking are to be reviewed and recorded on the Prior and Concomitant Medication CRF. Subjects will complete the GERD-HRQL questionnaire.

Subjects moving forward in the study will then be randomized to either undergo stimulation (Treatment Group) or no stimulation (Control Group). The subject and the treating physician and staff will be blinded to the randomization group assignment.

All subjects will then proceed to initial device stimulation setting procedures using the EndoStim Programmer. The same procedure will be followed for all subjects and device parameter settings will be completed by an unblinded technician using the EndoStim Programmer. For Treatment Group subjects, stimulation treatment parameters will be set per device nominal settings defined in Table 11. For Control Group subjects, the IPG will be programmed to the OFF mode so that no stimulation treatment is given. The final device settings for all participants will be documented.

Table 11. Implantable Pulse Generator Nominal Settings

Stimulation Parameters	Setting
Pulse Amplitude	5 mA
Polarity	Normal
Pulse Width	215 µsec
Pulse Rate (Frequency)	20 Hz
Impedance Tracker	Enabled
Impedance Tracker Recommended Values	Accepted
Dose Mode Parameters	Setting
Dose Schedule	00:00, 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00
Dose Time (Duration)	30 minutes
Block Time	60 minutes
On (Active) Time	N/A
Off (Inactive) Time	N/A
Duty Cycle	N/A
Sensing Parameters	Setting
Supine Time	N/A
Supine Level	N/A
Minute %	N/A
Supine Time %	N/A

Adverse events will be assessed and recorded. Diet and lifestyle instructions (Appendix B) will be provided and reviewed with the subject.

5.30 Blinded Phase, Treatment Group and Control Group

5.30.1

5.30.2

5.30.3

5.30.4

5.30.5

5.30.6 Blinded Phase, Office Visit, Month 1

On the one-month follow-up visit, subjects will undergo a routine physical examination, an adverse event assessment, and a review of medication use. GERD-HRQL and RSI questionnaires will be completed by the subject. The subject may discontinue use of the compression band after 30 days of use.

The implanted IPG device will be visually inspected for migration, tissue abrasion and erosion. The device will be interrogated and statistics downloaded to verify device functionality. No device setting changes will be made at this time. The final device settings for all participants will be documented.

Subjects will be asked to identify which treatment group they believe they have been assigned to using the following script:

"Please identify whether you believe you were assigned to the Treatment Group (immediate stimulation) or Control Group (delayed stimulation)."

The subject's response will be recorded.

Diet and lifestyle instructions (Appendix B) will be provided and reviewed with the subject.

5.30.7 Blinded Phase, Phone Interview, Month 2

The subject will be followed via a follow-up phone call at post-implant interval month two. GERD-HRQL and RSI questionnaires will be completed by the subject. Additionally, an adverse event assessment and medication use review will be completed.

At the discretion of the investigator, the subject may be asked to return for an office visit if needed. See Section 6.11 for Unscheduled Visit requirements.

In preparation for the 3-month office visit, the subject will be instructed in the use of the Subject Diary. Daily diary completion is required for a minimum of 10 days prior to required **off-PPI and H2** blocker evaluation period. Additionally, subjects will continue to complete the daily diary during the required **off-PPI and H2** blocker evaluation period of 10-14 days prior to the next office visit. During this off-medication time period, antacid use for symptom relief is allowed and will be documented by the subject in the Subject Diary.

5.30.8 Blinded Phase, Office Visit, Month 3 (Day 1)

Subjects will be contacted approximately 14 days prior to the three-month follow-up visit and reminded of the need to go **off PPI** 10-14 days prior to the visit. Subjects will be reminded to fast for approximately 8 hours prior to the office visit.

At the three-month follow-up visit, subjects will undergo a routine physical examination, an adverse event assessment, and a review of medication use. The completed Subject Diary and changes from the last visit will be reviewed with the subject. GERD-HRQL Heartburn and RSI questionnaires will be completed by the subject.

The implanted IPG device will be visually inspected for migration, tissue abrasion and erosion. The device will be interrogated and statistics downloaded to verify device functionality via the unblinded technician. The final device settings will be documented.

Female subjects of child-bearing potential must be on a reliable form of birth control and undergo a urine pregnancy test. Subjects found pregnant during the study will have the device turned off and will be discontinued from the study.

Subjects will undergo Bravo Esophageal pH probe placement at the end of the visit. The probe may be placed via endoscopy. The subject will be asked to continue **off-PPI and H2** blockers and to return the Bravo equipment for analysis as instructed by the site.

Diet and lifestyle instructions (Appendix B) will be provided and reviewed with the subject.

5.30.9 Blinded Phase, Office Visit, Month 3 (Day 3)

An in-person Day 3 visit is optional. Sites may elect to have the patient return the Bravo equipment via shipment per the site's instructions. Only pH data from the first 48 hours will be considered for this study. Any data collected beyond 48 hours will be disregarded. If the patient does not return to the clinic for this visit, a brief phone visit should be conducted to confirm the equipment was returned and any adverse events reported should be documented. The patient would need to return to the clinic after the pH results are available only if those results qualify the patient for device parameter optimization.

If indicated, device parameter optimization may be completed for Treatment Group subjects via the unblinded technician by switching device polarity if the total acid exposure is found to be above 5% or not reduced by 50% or more from baseline (on an acceptable day with the highest acid exposure percentage time); otherwise, no change in parameters is made. The final device settings will be documented. The Control Group will undergo sham device parameter optimization in the same fashion as the Treatment Group.

Adverse events will be assessed and recorded.

5.30.10 Blinded Phase, Phone Interview, Month 4

The subject will be followed via a follow-up phone call at post-implant interval month four. GERD-HRQL and RSI questionnaires will be completed by the subject. Additionally, an adverse event assessment and medication use review will be completed.

At the discretion of the investigator, the subject may be asked to return for an office visit if needed. See Section 6.11 for Unscheduled Visit requirements.

In preparation for the 6-month office visit, the subject will be instructed in the use of the Subject Diary. Daily diary completion is required for a minimum of 10 days prior to the next office visit and must be done outside of the required **off PPI and H2** blocker evaluation period. Additionally, subjects will continue to complete the daily diary during the required **off-PPI and H2** blocker evaluation period of 10-14 days prior to the next office visit. During this off-medication time period, antacid use for symptom relief is allowed and will be documented by the subject in the Subject Diary.

5.30.11 Blinded Phase, Office Visit, Month 6 (Day 1)

Subjects will be contacted approximately 14 days prior to the six-month follow-up visit and reminded of the need to go **off PPI** 10-14 days prior to the visit. Subjects will be reminded to fast for approximately 8 hours prior to the office visit.

At the six-month follow-up visit, subjects will undergo a routine physical examination, an adverse event assessment, and a review of medication use. The completed Subject Diary and changes from the last visit will be reviewed with the subject. Subjects will complete the following questionnaires:

- Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) Heartburn Questionnaire
- Reflux Symptom Index (RSI)
- Pittsburgh Sleep Quality Index (PSQI)
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI)
- Structured GI Symptoms (Structured GI)
- SF-12

The implanted IPG device will be visually inspected for migration, tissue abrasion and erosion. The device will be interrogated and statistics downloaded to verify device functionality via the unblinded technician. The final device settings will be documented.

Female subjects of child-bearing potential must be on a reliable form of birth control and undergo a urine pregnancy test. Subjects found pregnant during the study will have the device turned off and will be discontinued from the study.

Subjects will undergo the following laboratory tests: complete blood count, chemistry 7 panel or basic metabolic panel, and HbA1c.

Subjects will undergo endoscopy followed by Bravo Esophageal pH monitoring with endoscopic pH probe placement at the end of the visit. The subject will be asked to continue **off-PPI and H2** blockers and to return the Bravo equipment for analysis as instructed by the site.

Diet and lifestyle instructions (Appendix B) will be provided and reviewed with the subject.

5.30.12 Blinded Phase, Office Visit, Month 6 (Day 3)

Subjects will return the Bravo equipment as instructed by the site. Only pH data from the first 48 hours will be considered for this study. Any data collected beyond 48 hours will be disregarded.

Subjects will return to the site upon evaluation of the pH data. Subjects will undergo Esophageal HRM testing. Adverse events will be assessed and recorded.

Subjects will be asked to identify which treatment group they believe they have been assigned to prior to revealing the treatment assignment using the following script:

"Please identify whether you believe you were assigned to the Treatment Group (immediate stimulation) or Control Group (delayed stimulation)."

The subject's response will be recorded.

Subjects and clinicians will then be unblinded.

If indicated, device parameter optimization may be completed for Treatment Group subjects by switching device polarity if the total acid exposure is found to be above 5% or not reduced by 50% or more from baseline or suboptimal subjective symptom response; otherwise, no change in parameters is made. For Control Group subjects, stimulation treatment parameters will be set to the parameter values defined in Table 11. The final device settings will be documented.

In preparation for the 9-month office visit, the subject will be instructed in the use of the Subject Diary. Daily diary completion is required for a minimum of 10 days prior to the next office visit.

5.31 Open-Label Treatment Phase, Treatment Group

5.31.1 Open-Label Treatment Phase (Treatment Group), Office Visit, Month 9

Subjects will be contacted at least 10 days prior to the 9-month follow-up visit and reminded of the need to start completing the daily Subject Diary.

At the 9-month follow-up visit, subjects will undergo a routine physical examination, an adverse event assessment, and a review of medication use. The completed Subject Diary and changes from the last visit will be reviewed with the subject. GERD-HRQL and RSI questionnaires will be completed by the subject. The implanted IPG device will be visually inspected for migration, tissue abrasion and erosion.

The device will be interrogated and statistics downloaded to verify device functionality. At the investigator's discretion, Bravo Esophageal pH probe placement may be scheduled and completed. The probe may be placed via endoscopy. If indicated by the pH results, device parameter optimization may be completed by switching device polarity if the total acid exposure is found to be above 5% or not reduced by 50% or more from baseline or suboptimal subjective symptom response; otherwise, no change in parameters is made. The final device settings will be documented.

Female subjects of child-bearing potential must be on a reliable form of birth control and undergo a urine pregnancy test. Subjects found pregnant during the study will have the device turned off and will be discontinued from the study.

Diet and lifestyle instructions (Appendix B) will be provided and reviewed with the subject.

In preparation for the 12-month office visit, the subject will be instructed in the use of the Subject Diary. Daily diary completion is required for a minimum of 10 days prior to the next office visit and must occur outside of the required **off PPI and H2** blocker evaluation period. Additionally, subjects will continue to complete the daily diary during the required **off-PPI and H2** blocker evaluation period of 10-14 days prior to the next office visit. During this off-medication time period, antacid use for symptom relief is allowed and will be documented by the subject in the Subject Diary. The subject will be reminded to fast for approximately 8 hours prior to the Bravo probe placement at the next visit.

5.31.2 Open-Label Treatment Phase (Treatment Group), Office Visit, Month 12

Follow same visit requirements for the Blinded Phase, Office Visit, Month 6 noted in Sections 6.7.6 and 6.7.7 (with the exception of Esophageal Manometry which is not required). Note: Diagnostic endoscopy testing is only required in subjects who had esophagitis at their 6-month visit. An endoscopy may be performed to aid in the placement of the Bravo capsule.

The device will be interrogated and statistics downloaded to verify device functionality. If indicated by the pH results or suboptimal subjective symptom response, device parameter settings may be changed in the following order:

- Change polarity (Omit this step if polarity was changed during a previous visit.)
- Change to alternating polarity and increase the number of sessions per day
- Increase pulse amplitude.

The final device settings will be documented. Device parameter settings will be addressed in this manner at all future follow-up visits (i.e., 12 months post-stimulation and later).

5.31.3 Open-Label Treatment Phase (Treatment Group), Phone Visit, Month 18

The subject will be followed via a follow-up phone call at post-implant interval month 18. GERD-HRQL and RSI questionnaires will be completed by the subject. Additionally, an adverse event assessment and medication use review will be completed.

At the discretion of the investigator, the subject may be asked to return for an office visit if needed. See Section 6.11 for Unscheduled Visit requirements.

5.32 Open-Label Treatment Phase, Control Group

5.32.1 Open-Label Treatment Phase (Control Group), Office Visit, Month 7 (1 Month of Stimulation)

Follow same visit requirements for the Blinded Phase Post-Implant Office Visit Month 1 noted in Section 6.7.1.

5.32.2 Open-Label Treatment Phase (Control Group), Phone Interview, Month 8 (2 Months of Stimulation)

Follow same visit requirements for the Blinded Phase Post-Implant Phone Interview Month 2 noted in Section 6.7.2.

5.32.3 Open-Label Treatment Phase (Control Group), Office Visit, Month 9 (3 Months of Stimulation)

Follow same visit requirements for the Blinded Phase Post-Implant Office Visit Month 3 noted in Sections 6.7.3 and 6.7.4. Note that Bravo is optional based on symptoms.

5.32.4 Open-Label Treatment Phase (Control Group), Phone Interview, Month 10 (4 Months of Stimulation)

Follow same visit requirements for the Blinded Phase Post-Implant Phone Interview Month 4 noted in Section 6.7.5.

5.32.5 Open-Label Treatment Phase (Control Group), Office Visit, Month 12 (6 Months of Stimulation)

Follow same visit requirements for the Blinded Phase Post-Implant Office Visit Month 6 noted in Sections 6.7.6 and 6.7.7. Note that diagnostic endoscopy is only required if esophagitis was reported at Month 6. An endoscopy may be performed to aid in the placement of the Bravo capsule.

The device will be interrogated and statistics downloaded to verify device functionality. If indicated by the pH results or suboptimal subjective symptom response, device parameter settings may be changed in the following order:

- Change polarity (Omit this step if polarity was changed during a previous visit.)
- Change to alternating polarity and increase the number of sessions per day
- Increase pulse amplitude.

The final device settings will be documented. Device parameter settings will be addressed in this manner at all future follow-up visits (i.e., 12 months and later).

5.32.6

5.32.7 Open-Label Treatment Phase (Control Group), Office Visit, Month 15 (9 Months of Stimulation)

Follow same visit requirements for the Open-Label Treatment Phase (Treatment Group) Office Visit Month 9 noted in Section 6.8.1.

5.32.8 Open-Label Treatment Phase (Control Group), Office Visit, Month 18 (12 Months of Stimulation)

Follow same visit requirements for the Open-Label Treatment Phase (Treatment Group) Office Visit Month 12 noted in Section 6.8.2.

5.32.9 Open-Label Treatment Phase (Control Group), Phone Visit, Month 24 (18 Months of Stimulation)

Follow same visit requirements for the Open-Label Treatment Phase (Treatment Group) Office Visit Month 18 noted in Section 6.8.3.

5.33 Open-Label Extended Follow-Up Phase

5.33.1

5.33.2 Open-Label Extended Follow-Up Phase, Office Visit, Annual Follow-up Visits

Annual office visits will occur for 5 years post-stimulation for all subjects. Annual office visits will be calculated relative to the date of stimulation turn-on for each subject, ± 30 days. In the event of FDA approval or study closure by the sponsor, this duration may be shortened at the discretion of the sponsor.

Subjects will be contacted prior to the annual follow-up visit and reminded of the need to start completing the daily Subject Diary. Subject Diary completion is required a minimum of 10 days prior to the annual visit.

At each annual visit, subjects will undergo a routine physical examination, an adverse event assessment, and a review of medication use. The completed Subject Diary will be reviewed with the subject and changes will be reviewed. Subject questionnaires will be provided to the subject:

- Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) Heartburn Questionnaire
- Reflux Symptom Index (RSI)
- Pittsburgh Sleep Quality Index (PSQI)
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI)
- Structured GI Symptoms (Structured GI)
- SF-12
- Healthcare Resource Utilization

The implanted IPG device will be visually inspected for migration, tissue abrasion and erosion. The device will be interrogated and statistics downloaded to verify device functionality. Device parameter settings may be changed as described in section 6.8.2. The final device settings will be documented.

Female subjects of child-bearing potential must be on a reliable form of birth control and undergo a urine pregnancy test. Subjects found pregnant during the study will have the device turned off and will be discontinued from the study.

Diet and lifestyle instructions (Appendix B) will be provided and reviewed with the subject.

5.34 Unscheduled Visits

An unscheduled visit is a visit that occurs outside of a study-required visit window or an additional visit that occurs within a study-required visit window. Minimum data collection requirements for unscheduled visits may include: adverse event assessment, medication use, and device parameters.

5.35 Non-Response to Investigational Treatment

After diligent assessment of stimulation parameters and appropriate use of rescue medications, if the subject and physician believe that the electrical stimulation treatment has not generated sufficient symptom control to warrant continued treatment, electrical stimulation will be stopped, the subject will be considered treatment failure for the purposes of analysis, and the device system will be either turned off and/or removed per Section 6.13.

5.36 Therapy Discontinuation and Follow-up

To discontinue EndoStim LES Stimulation therapy, the device may be turned off and may remain implanted at the discretion of the investigator and subject. If it is determined that the lead and/or IPG needs to be explanted, including at the completion of the study, the subject will be admitted for the device and/or lead removal procedure as noted in the EndoStim Clinician Manual.

Following the procedure, the subject will be recovered using standard institutional protocol and then discharged home. Approximately 1 week following the procedure, the subject will be seen by the investigator for evaluation of the wound and suture removal, will undergo a physical examination and potential adverse events will be assessment. The subject will be monitored by a phone interview approximately one year (+/- 30 days) after the explant procedure to assess potential adverse events, medication use, GERD symptoms (via GERD-HRQL) and healthcare resource utilization. Any additional treatment required to manage GERD will be outside the scope of the study and at the discretion of the subject's physician. After device explant and the 1-year follow-up, there are no additional clinic visits or follow-ups in the study. The subject will then be discontinued from the study and transferred by the study physician to an appropriate ongoing standard of care therapy.

5.37 Implanted Device Replacements

Although implanted device replacements are not anticipated, if needed, device replacements will be completed per the respective device explant and implant sections of the EndoStim Clinician Manual. The clinical investigator will record device replacements per Section 7 below. The subject may continue to be followed per the original follow-up schedule. Explanted devices should be returned to EndoStim for analysis.

5.38 Post Study

Subjects may consult with their physician regarding EndoStim LES Stimulation System therapy continuation after the study closes. Alternatives include:

- Continue therapy – be followed on a regular basis per standard of care as recommended by treating physician
- Discontinue therapy:
    - IPG turned off, system remains implanted
    - IPG and/or lead explanted within 3 months of study closure (per section 6.13)

7. ADVERSE EVENTS

All new or worsening adverse events (AEs) will be collected for all subjects from the time of subject enrollment through completion or termination of the clinical investigation. This includes AEs that are not device or procedure related.

The investigator will report adverse events using the Adverse Event CRF as soon as possible upon awareness. All adverse events should be followed until the adverse event has been resolved or until study closure, whichever occurs first. Report each adverse event on a separate Adverse Event CRF.

7.6.1 Definitions

Adverse Event
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects whether or not related to the investigational medical device.

5.38.1
Unanticipated Adverse Events
An unanticipated adverse event is an adverse event that has not been previously identified in nature, severity or degree of incidence in the clinical investigational plan, subject informed consent form, risk management reports, the Report of Prior Investigations, applicable published literature, or the product labeling.

Adverse Event Severity
Each adverse event will be classified as a Serious Adverse Event, Non-Serious Adverse Event, or an Observation.

Serious adverse events (SAEs) are defined as those events that:
a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, or
   3) in-patient admission or prolonged hospitalization, or,
   4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.

A Non-Serious Adverse Event is defined as an event which does not meet the definition of a serious adverse event but is still an undesirable clinical occurrence and is a negative change from baseline, whether or not device related.

Observation is a subset of adverse events that are usually transient and do not require clinician prescribed intervention. The event does not generally interfere with usual activities of daily living (e.g. fatigue, common cold, strained muscle).

Adverse Event severity will be categorized as follows:

Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Severe: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.

Adverse Event Relatedness Determination
The causal relationship between the event and the EndoStim LES Stimulation System and the implant or explant procedure will be classified by the CEC using the following guidelines:

- Device Related: An adverse event that results from the presence or performance of the IPG, Lead, and/or Programmer under investigation.
- Implant Procedure Related: An adverse event that occurs due to the implant or explant procedure during or within 30 days of the procedure and was not directly caused by the EndoStim LES Stimulation System under investigation.
- Study-Procedure Related: An adverse event that results from a study-required testing and is not related to the implant procedure.

Relatedness will be categorized by the Investigator as one of the following:

- Definite: An adverse event that has a timely relationship to the administration of the study procedure and follows a known pattern of response for which no alternative cause is present

- Probable: An adverse event that has a timely relationship to the administration of the study procedure and follows a known pattern of response, but for which a potential alternative cause may be present
- Possible: An adverse event that has a timely relationship to the administration of the study procedure, follows no known pattern of response, but a potential alternative cause does not exist
- Not Related: An adverse event for which there is evidence that it is definitely related to a cause other than the investigational study procedure; in general, no timely relationship to the administration of the procedure exists, or if so, the event does not follow a pattern of response and an alternative cause is present

Adverse Event Timing
The timing of the event relative to the implant procedure will be defined for each adverse event using the following guidelines:

- Pre-Implant: An adverse event that occurs after the Subject Informed Consent has been signed, but before the first skin incision during implant.
- Implant/Explant: An adverse event that occurs during implant/explant prior to completion of final skin closure.
- Post-Implant/Explant: An adverse event that occurs after implant/explant final skin closure.

Unanticipated Adverse Device Effect (UADE)
Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The DMC will make the determination if an event meets the definition of a UADE. A

Adverse Event Classification for Primary Safety Objective

The CEC will adjudicate all adverse events for relationship to device/implant/study procedure and for serious/non-serious categorization. Adjudication will be done according to the board charter. The outcome of these adjudications will be used for the primary safety objective.

8. TECHNICAL OBSERVATIONS

A Technical Observation is defined as a failure or malfunction of the device, or a device/system functioning not according to design intent. It may also relate to inadequacies in the clinician manual, identification, durability, reliability, or performance.

9. RISK/BENEFIT ANALYSIS

1.1 Benefit

Results from this study are expected to contribute significantly to the evaluation of electrical stimulation for the treatment of GERD. In addition, 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. Subjects in both groups are expected to benefit from the LES stimulation therapy. Subjects assigned to the Control Group are expected to have a delayed potential benefit of GERD treatment for 6 months.

1.2 Potential Adverse Events and Risks

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 laparoscopic electrode placement, etc.).

Possible risks associated with the laparoscopic procedure include: unstable blood pressure, vertigo, hematoma, seroma, injury to organs, blood vessels or other structures, internal bleeding, bleeding from the incisions, blood clot, nerve damage, tissue perforation, abrasion or erosion, injury to organs within the abdominal cavity, wound separation, intravenous site complications, partial or complete blockage of the bowel, inflammation, infection, fever, adhesions, pneumonia, cardiac arrhythmia, cardiopulmonary depression, incisional hernia, sleep problems (insomnia), excess salivation, hiccups, dysphasia, bloating, belching, dyspepsia, early satiety/eating less, worsening pre-existing psychiatric illness, pain or discomfort related to the surgical procedure. Rarely, the gas that is passed to the abdomen can cause heart, lung or chest complications. Some of these events, if they were to occur, may require medicines, fluid replacement, blood transfusion, and/or another surgery to treat the event. In some cases, hospitalization may be required for further evaluation and treatment. Death as a result of this procedure is possible. **Possible anesthesia risks** include but are not limited to nausea, vomiting, fever, hypoxia, pneumonia, adverse drug reactions, urine retention, clumsiness, drowsiness, blurred vision, and death.

Right after the procedure, subjects may experience bloating or bruising and/or pain around the incisions, shoulder pain, sore throat, and cramping in the stomach. In some subjects, healing of the wound may be abnormal and the wound can be thickened and red and the scar may be painful.

The EndoStim Clinician Manual lists warnings, precautions, and potential adverse events related to the implant procedure and use of the EndoStim system. The EndoStim Patient Manual lists risks associated with other procedures required in the study such as blood draws, endoscopy, manometry, and pH testing.

Potential adverse events and risks will be mitigated by the following:

- Adherence to this study protocol and applicable local laws and regulations
- Provision of study protocol training to investigational site staff
- Selection of experienced laparoscopic surgeons

- Adherence to standard laparoscopic techniques
- Provision of EndoStim implantation procedure surgical training and proctoring
- Adherence to the EndoStim Clinician Manual
- Proper subject selection
- Subject monitoring during and after the procedure prior to discharge
- ECG monitoring during the first stimulation session
- Regular implant system physical and technical assessments
- Subject monitoring throughout the follow-up period by office visits and phone interviews
- Use of both subjective and objective subject assessment measures
- Regular clinical monitoring of clinical sites by EndoStim and/or EndoStim representatives

10. STATISTICAL METHODS AND DATA ANALYSIS

2.1 Adaptive Design

This is a two-armed, randomized, Bayesian adaptive trial designed to evaluate the safety and efficacy of the EndoStim LES Stimulation System. Patients will be randomized 1:1 to active treatment or sham control. This trial will implant a minimum of 120 and a maximum of 200 patients. Sample size selection interim analyses are planned to determine the trial's actual sample size between this minimum and maximum.

The details of the adaptive sample size plan are described in a separate document.

2.2 Endpoints

2.2.1 Primary Safety Endpoint

Objective: The primary safety endpoint will be the rate of occurrence of device- and/or procedure-related serious adverse events at the 12-month follow-up visit as adjudicated by the Clinical Events Committee.

Determination of Subjects for Primary Safety Analysis: All subjects who have been implanted with the EndoStim device will be included.

Analysis Methods: For each category of serious adverse event, the rate of occurrence and an exact 95% two-sided confidence interval will be computed.

2.2.2 Primary Efficacy Endpoint

Objective: Comparison between the treatment and the control group of the percentage (%) of subjects achieving pH success defined as normalization (pH < 4 for no more than 5.3% of monitoring time) or $\geq$ 50% improvement in their distal esophageal acid exposure compared to their baseline **off-PPI/H2** blocker distal esophageal pH at six months.

Hypothesis: The treatment group will have a higher success rate (normalization) than the control group.

Sample Size Justification: In preliminary non-randomized studies, 73% (19/26) subjects achieved the pH success criteria. We assume that we will see some attenuation of this rate due to blinding and plan for a treatment group success rate of between 60% and 70%. We conservatively assume that the control group will experience somewhere between 20% and 40% success rate.

The trial was simulated under 18 different response rates in order to characterize and evaluate the performance of the adaptive design. There were nine null scenarios where the response rate was the same in the treatment and control and nine scenarios where the response rate in the treatment was higher than the control. All scenarios are based on 10,000 simulations.

The table below shows the results of those simulations (Table 12). The columns are representing the following 1) the simulated control rates, 2) the simulated treatment rates, 3) the overall probability of success (power/Type I error), 4) the mean trial size, 5) the total probability that the trial achieves an early success, 6) the total probability that the trial stops early for futility, and 7) the probability that the trial is stopped for expected success and yet does not achieve success at the final analysis with complete follow-up data ("Flip Flop").

The results in the alternative models have a maximum simulated Type I error of 2.5% with a probability greater than 0.50 of stopping early for futility under the null. If treatment demonstrates superiority over control, the adaptive design offers the opportunity to identify this benefit with a sample size of less than 200 patients.

Based on these scenarios, at the smallest of the conservative differences based in the preliminary studies of 20%, with 180 patients the study has just under an 80% chance of success for the primary efficacy endpoint. As the difference between the groups increases, then the study will be above an 80% chance of success with the full 180 patients.

Table 12: Virtual Patient Response

Scenarios	Control Response Rate	Treatment Response Rate	**Prob. of Success**	**Mean Trial Size**	**Prob. of Stopping Early for Success**	**Prob. of Stopping Early for Futility**	**Prob. Of Success to Futility Flip Flop**
Null 1-1	0.1	0.1	0.021	179.0	0.004	0.512	0.004
Null 2-2	0.2	0.2	0.023	177.1	0.005	0.519	0.011
Null 3-3	0.3	0.3	0.023	176.6	0.006	0.515	0.013
Null 4-4	0.4	0.4	0.023	176.5	0.005	0.515	0.014
Null 5-5	0.5	0.5	0.024	175.8	0.007	0.526	0.015
Null 6-6	0.6	0.6	0.024	176.1	0.006	0.518	0.016
Null 7-7	0.7	0.7	0.025	176.7	0.006	0.520	0.013

Null 8-8	0.8	0.8	0.022	176.9	0.005	0.522	0.011
Null 9-9	0.9	0.9	0.020	178.7	0.003	0.519	0.004
Alternate 2-6	0.2	0.6	0.999	142.8	0.965	0.001	<0.0001
Alternate 2-7	0.2	0.7	>0.999	132.4	0.997	<0.0001	<0.0001
Alternate 3-6	0.3	0.6	0.982	161.1	0.760	0.003	0.006
Alternate 3-7	0.3	0.7	>0.999	143.8	0.956	<0.0001	<0.0001
Alternate 4-6	0.4	0.6	0.779	180.4	0.361	0.030	0.022
Alternate 4-7	0.4	0.7	0.983	161.2	0.758	0.003	0.004
Alternate 5-6	0.5	0.6	0.262	187.0	0.076	0.178	0.032
Alternate 5-6.5	0.5	0.65	0.535	186.0	0.186	0.079	0.032
Alternate 5-7	0.5	0.7	0.796	180.2	0.369	0.028	0.023

Determination of Subjects for Primary Efficacy Analysis: All subjects who have been randomized will be included.

Analysis Methods: The analysis for the primary efficacy endpoint will compare the success rates between the treatment and control using a logistic regression. The primary predictor of interest will be a dummy variable for active vs. sham treatment. The model will also control for crural approximation as this is potentially an independent predictor of treatment success. The primary efficacy endpoint will be satisfied if the one-sided p-value for the primary predictor is less than 0.022. We will conduct additional analyses adjusting for other important baseline characteristics.

2.2.3 Secondary Endpoints

Analysis Methods: There are three types of secondary endpoints: (a) comparison of arms from the sham-controlled trial (blinded), (b) success from the open label trial (open label), and (c) estimation of adverse events across the entire trial with no test statistics (secondary safety estimation).

For the endpoints of type (a, blinded) we will compare either the mean values (for continuous measures) using two-sample t-tests or the proportion of successful subjects (for binary measures) using Fisher's exact test. For the endpoints of type (b, open label), we will judge success based on the improvement at the 12-month time point for the treatment arm and the 18-month time point for the sham arm (i.e. after 12 months of stimulation) from their baseline values. Assuming that these data are judged to be poolable between the two arms (see section 10.6 below), we will construct a one-sided confidence interval and then determine whether the lower confidence limit exceeds the null success rate of 60%. For endpoints of type (c, safety estimation) if groups are determined to be poolable, we will create one estimate across all patients, otherwise we will create an estimate within each arm. If the ITT and safety dataset are different then the safety dataset will be utilized, otherwise the ITT will be the primary dataset for the secondary safety endpoints.

As we will be performing multiple hypothesis tests for the secondary endpoints, we will need to correct for multiple comparisons. We note that the simple Bonferroni correction (which would adjust all p-values by dividing 14, for the number of secondary endpoints) would be inappropriately punitive as the endpoints are likely to be strongly correlated. Instead we propose to adjust the p-values (confidence limits) by the bootstrap method of Westfall (as implemented in SAS Proc Multtest).[22] This will result in a level of adjustment that is appropriate for the correlation of the endpoints, but will strictly preserve the family-wise type I error rate at the 0.025 level.

Power Considerations: Although we will not be analyzing the data with Bonferonni correction, we conservatively use this for power considerations and note that actual power is likely to be much higher with the bootstrap correction. Thus, we conservatively assume that each endpoint is to be tested at a one-sided alpha of

0.025/14 = 0.0018. For the open-label endpoints, we would thus require a 99.65% one-sided confidence interval for the true success percentage to have a lower bound that exceeds 60%. For a particular secondary endpoint with true success rate of 76%, we would have 80% power to reject the null hypothesis that the success rate was 60% or lower. We have preliminary data available on most of the secondary endpoints and the observed success rates are listed in Table 13.

Table 13: Secondary Endpoints and Preliminary Success Rates

Open-Label Secondary Endpoints	Number Successes or Subjects	Success Rate
Number of subjects achieving GERD symptom success defined as an improvement in their total GERD-HRQL score of 50% or more compared to their baseline **off-PPI and H2** blocker GERD-HRQL Score	26/27	96%
Number of subjects achieving GERD symptom success defined as an improvement in their total GERD-HRQL score of 50% or more compared to their baseline **on-PPI and H2** blocker GERD-HRQL Score	21/27	78%
Number of subjects achieving supine pH success defined as normalization of pH (pH < 4 for no more than 1.4% of supine period) or $\geq$ 50% improvement in their supine distal esophageal acid exposure compared to their baseline **off-PPI and H2** blocker distal esophageal supine pH	20/25	80%
Number of subjects able to stop regular use of acid-suppression medication (defined as 50% or more Subject Diary days without PPI or H2 blocker use)	25/26	96%
Number of subjects able to stop all use of acid-suppression medication (defined as 100% Subject Diary days without PPI or H2 blocker use)	23/26	88%
Number of subjects reporting 50% or more reduction in severity of heartburn symptoms as measured by daily Subject Diary	18/21	86%
Number of subjects reporting 50% or more reduction in severity regurgitation symptoms as measured by daily Subject Diary	20/20	100%
Number of subjects reporting 50% or more reduction in nocturnal symptom of heartburn as measured by daily Subject Diary	18/21	86%
Number of subjects reporting 50% or more reduction in nocturnal symptom of regurgitation as measured by daily Subject Diary	19/20	95%
Number of subjects reporting 50% or more improvement in sleep-related quality of life as measured by the Pittsburgh Sleep Quality Index (PSQI)	26/27*	96%

* PSQI not measured in CS004 and not available for CS005 at time of analysis. Data is presented from the GERD-HRQL individual sleep question.

This suggests the study would be strongly powered for 9 of the 10 open-label secondary endpoints and better than 50% powered for the remaining endpoints.

For the blinded-phase secondary endpoints, we consider the power for the case where the blinded-phase portion of the trial is stopped after 120 total subjects. Power would of course increase if the study continued longer. In the event that the study stopped sooner, the data will likely be strongly in favor of the Treatment Group for many of the secondary endpoints since they are strongly related to pH.

Even a conservative estimate at minimum recruitment, 120 subjects divided evenly into Control and Treatment Groups, we will be 80% powered using the overly conservative one-sided level of 0.0018 to detect a 0.7 standard deviation difference between the two arms for continuous endpoints and 80% powered to detect a difference in success rate of approximately 25 to 35 percentage points (e.g. Control Group 33%, Treatment Group 66%; Control Group 68% vs. Treatment Group 93%).

We note that many of the continuous endpoints improved from Baseline to Follow-up by 1 or more standard deviations. For example, mean percentage of time distal esophageal pH is <4.0 improved from 10.8% (5.1%) to 5.3% (4.9%) with the difference better than 1 SD. HRQL improved from 10.8 (7.3) to 3.1 (3.9), with the difference equal to 1 SD; heartburn symptom score from 1.9 (0.5) to 0.4 (0.6), better than 2 SD; similar magnitude in improvements seen for nocturnal heartburn and regurgitation and for levels of GERD medication use. This suggests that we would be adequately powered to see a difference even if the placebo effect was substantial. For the binary endpoints of GERD improvement/control and nocturnal GERD improvement/control, we would be 80% powered if the true rates are 70% treatment (as in our preliminary data) vs. 33% control and 55% powered for 70% vs. 40%.

10.2.4 Crural Approximation

An important subgroup analysis will be to compare treatment effects in subjects who underwent crural approximation versus those that did not. The estimates of treatment differences from these stratified analyses will be of clinical interest. Formal tests for subgroup heterogeneity will be conducted by including an interaction of the treatment arm indicator and the subgroup factor in models for the primary and secondary outcomes.

10.2.5 Other Subgroup Analyses

In addition, we will compare several pre-specified subgroups of clinical interest to examine the heterogeneity of treatment effect including age (<65 vs $\geq$65), gender (male vs. female), race /ethnicity (White vs. non-White), BMI (<25, 25-30, $\geq$30), hiatal hernia status (hernia, no hernia). Formal tests for subgroup heterogeneity will be conducted by including an interaction of the treatment arm indicator and the subgroup factor in a logistic regression model with pH success as the outcome.

10.3 Subject Disposition

The number of subjects that enter, enroll, and complete or discontinue from the study will be presented.

10.4 Subject Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized overall and by treatment arm. Descriptive summaries will include the number of subjects, mean, standard deviation, median, minimum and maximum for continuous parameters, frequencies and percentages for categorical parameters. Wilcoxon rank sum tests will be used to compare continuous characteristics between arms and chi-squared tests to compare categorical characteristics between arms.

10.5 Maintenance of Blinding

Subjects will be asked at 1 month and at 6 months to guess their treatment allocation. The percentage of subjects that guess correctly will be tabulated overall and by arm. A comparison between arms will be made using a chi-squared test.

10.6 Poolability of Data

Subject demographics will be collected and summarized by geography. ANOVA and chi-squared analyses will be used to test for site and geography (US vs. OUS) differences in demographics. To test for site/geographic poolability of the data, we will examine forest plots of the site-specific and geography-specific estimated treatment effects. Formal tests for poolability will be conducted by including an interaction of (i) site and treatment arm and (ii) geography by treatment arm in our model. Sites with fewer than 5 subjects will be grouped together for analysis purposes.

For all endpoints, we will examine: (i) for the control subjects, the change from baseline (T1) to the 18 month visit (T2), and (ii) for the treatment subjects, the change from baseline (T1) to the 12 month visit (T2). As the control subjects are unblinded for full duration of their 12 month treatment and the treatment subjects are unblinded for half (6 month) duration of their 12 month treatment, there may be a potential concern as to the poolability of the 2 groups for describing 12-month therapy effect, especially on outcomes that may be susceptible to the sham effect. We do not believe that these differences will have any clinically meaningful impact on these outcomes. However, to address any such concerns we propose the following design:

(1) A test for homogeneity of treatment and control patient's outcomes at both T1 and T2. We will use a two sample t-test to compare the group means; poolability will be accepted if both the t-tests have p-values $\geq$ 0.10.

(2) if poolability accepted in 1, then pool subjects to compute estimate and two sided confidence interval (alpha to be determined from the Westfall method of multiple testing, as described in Section 10.2.3) for overall success rate for that specific outcome after 12 months on treatment. Should the lower bound of the confidence interval exceed 60%, then the endpoint will be met.

(3) if poolability not accepted in 1, then compute estimates and two sided confidence interval (alpha to be determined from the Westfall method of multiple testing, as described in Section 10.2.3) for overall success rate after 12 months on treatment separately in each group. Should the lower bound of both confidence intervals exceed 60%, then the endpoint will be met.

11. STUDY CONDUCT

3.1 Study Initiation

Prior to the initiation of the clinical investigation, the qualifications of the Principal Investigator and staff, and adequacy of the clinical investigation sites shall be verified and documented. Prior to initiating patient enrollment at the investigational site, EndoStim or a designee will provide training on the clinical investigation plan to the Principal Investigator. EndoStim or a designee will additionally provide training to site staff as requested by the Principal Investigator. Before a site is allowed to enroll patients, study preparation documents required by EndoStim's quality system must be completed and received.

3.2 Governance

3.2.1 Study Principal Investigator

EndoStim may appoint an overall Study Principal Investigator who serves in an advisory capacity throughout this study and is a participating Investigator in the study. The person in this role will oversee and monitor study committees and boards, and provide input into study procedures and methodology as requested.

3.2.2 Steering Committee

A physician Steering Committee may be utilized to serve in an advisory capacity throughout this study providing input into the study methodology, study execution, questions of medical practice standards of care, subject-related questions, clinical issues, interactions with trial investigators, regulatory agencies, and other stakeholders, and provide guidance on data analysis and interpretation. Members of the committee can be investigators in this study.

3.2.3 Data Committees

3.2.3.1 Clinical Events Committee (CEC)

An independent CEC will review all adverse events reported in this study. Reviews will be conducted according to the CEC charter. Members of the committee cannot be investigators in this study.

3.2.3.2 Data Monitoring Committee (DMC)

An independent DMC will review overall study progress, as well as review unblinded data sets (prepared by an unblinded trial statistician who is employed by an independent third-party) for safety oversight and at various interim analyses and advise the company accordingly. The DMC will operate under the DMC charter. Members of the committee cannot be investigators in this study.

3.2.4 Independent Review Committees

Each center will obtain local Institutional Review Board or Medical Ethics Committee (IRB or MEC) approval of this study protocol and informed consent prior to commencement of subject enrollment, and remain under the administration of an IRB or MEC throughout the duration of the study.

3.3 Investigator Agreements and Financial Disclosure

Each investigator will sign an Investigator Agreement and provide financial disclosure prior to their participation in the study. Investigators must inform EndoStim of any changes to financial interests throughout the course of the study and for a period of one year following the completion of the study.

3.4 Data Management

Source documents shall be maintained by the investigational sites throughout the course of the investigation. All findings in this investigation must be documented as source data, and therefore can be verified (and audited). Source documentation may be paper or electronic, and is defined as the first time the data appears and may include for example; all questionnaires, phone interview notes, clinical records, hospital records, surgery reports, death/autopsy reports, and any other material that contains original information used for clinical study data collection or adverse event reporting. It should be possible to verify the inclusion and exclusion criteria for the investigation from available source data.

Subject data will be submitted to EndoStim using a web-based electronic data capture system maintained by EndoStim. Designated site personnel will access the database online and be given access to enter/review/modify data for their respective site/subjects. Each electronic CRF (eCRF) should be fully complete as soon as possible after the subject's visit. If additional documentation (e.g., clinic or procedural notes, adverse event summaries, test reports) are required for any reason it must be appropriately redacted to block the subject's name and any additional identifying information, and the subject's unique study ID code inserted, prior to being sent to EndoStim.

EndoStim and investigational sites will retain study-related documents per EndoStim and local regulatory requirements, but in no case shorter than a period of 2 years after the termination or completion of the clinical investigation, or the date that records are no longer required for purposes of supporting a premarket approval application. The Principal Investigator or EndoStim may transfer custody of records to another person or entity and will document the transfer accordingly.

3.5 Subject Completion of the Study

An Early Discontinuation or Study Completion CRF is required for each enrolled subject. Study completion may be requested by the subject, clinical investigator, or sponsor.

- Subject Request: The subject will be exited from the study in the event that a subject is unable to participate, expresses a desire to withdraw, or is unwilling to continue

participation in the study. The clinical investigator should inform the subject that future care or treatment will not be affected in any way as a result of choosing to not participate in this study. The clinical investigator should also discuss the alternative treatment and medical consequences of exiting the study. The clinical investigator will notify the subject of any significant new findings that may develop about the EndoStim LES Stimulation System during the course of the study, which may relate to the subject's willingness to continue participation.

- Clinical Investigator Request:
  - Medical Necessity: The subject may be exited from the study if the clinical investigator feels it is necessary to withdraw the subject from the study due to a medical condition or other reason. The clinical investigator must notify the subject and EndoStim, as well as provide an explanation regarding the reasons for the study exit.
  - Screen Failure: Subjects who sign an Informed Consent, however subsequently do not meet all of the study inclusion/exclusion criteria.
  - Unsuccessful Implant Attempt: If an implant is attempted, but is unsuccessful and no further implant attempts are planned, the subject will be exited from the study. However, if there are ongoing adverse device or study procedure-related effects, they will be followed until the event has been resolved.
  - Device Explant: If a system modification requires a device/system explant without replacement, the subject will be exited from the study. If there are ongoing adverse device effects, they will be followed until the event has been resolved.
  - Lost to Follow-up: If the subject fails to comply with at least 2 consecutive follow-up visits, the study center must make attempts to contact the subject. Details of a minimum of two attempts and the method of attempt (e.g. one letter and one phone record or two letters) to contact the subject must be documented in the subject's records.

- Sponsor Request: If the sponsor suspends study enrollment at a center and a subject has signed the Subject Informed Consent, but no implant attempt of the investigational system has occurred, the subject may be exited from the study. If the subject has any condition that, at the discretion of the sponsor, would interfere with accurate interpretation of the study endpoints or preclude participation in the trial, EndoStim must notify the investigator to provide an explanation regarding the reasons for recommending the study exit.

If a subject's exit from the study is related to an issue of safety or clinical performance of the investigational system, or if the subject has any unresolved adverse device effects at the time of study exit, the center must attempt to follow-up with the subject according to the subject's follow-up schedule, unless or until the issue is resolved, or at study closure (as defined below), whichever occurs first. The follow-up to an adverse event update may be made by telephone. The clinical investigator will document the follow-up attempts on the Early Discontinuation or Study Completion CRF.

3.6 Monitoring

Trained personnel appointed by EndoStim will conduct monitoring activities and ensure that the investigation is conducted in accordance with this study protocol, signed Investigator Agreement, Clinical Trial Agreement, and applicable regulatory requirements of the country in which the study is conducted. The monitor's qualifications and training will be documented and kept on file by EndoStim.

Monitoring visits will occur based on implant rate and volume, duration of the study, study compliance at each center, and any suspected inconsistency in data that requires investigation. Monitoring will be performed according to an approved study-specific Monitoring Plan. Device storage and accountability will be assessed during clinic site visit(s). The monitor must prepare a formal written report following each visit and supply the site with a summary of findings.

Study closure visits will be conducted with all sites that have enrolled patients for the purpose of reviewing record retention requirements, product disposition requirements, etc. A telephone contact may take the place of a study closure visit if appropriate (e.g., low subject enrollment, recent monitoring visit, etc.).

3.7 Study Deviations

A study deviation is defined as an event within a study that did not occur according to the study protocol, instructions, applicable laws or regulations or the Clinical Trial Agreement. All deviations will be recorded, together with an explanation for the deviation, on the Protocol Deviation CRF. Each Principal Investigator is responsible for ensuring accurate, complete, and current records, including documentation showing the date, reason, and status of every deviation from the study protocol.

Prior approval by EndoStim is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. This prior approval should be recorded in the subject's file or on the Protocol Deviation CRF. To obtain approval, contact EndoStim to discuss potential deviations.

Prior approval is not required when a deviation is necessary to protect the life or physical well-being of a subject in an emergency. Prior approval is not expected in situations where unforeseen circumstances are beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent errors, equipment failure, or inability to perform required procedures due to subject illness).

Study deviations must be reported to EndoStim, regardless of whether medically justifiable, pre-approved by the trial leader, or taken to protect the subject in an emergency. In the case that the deviation involves a failure to obtain subject informed consent or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the Institutional Review Board (IRB)/Medical Ethics Committee (MEC) as well as the sponsor within 5 working days. Reporting of all other study deviations should comply with IRB/MEC policies and/or local laws.

3.8 Clinical Investigational Plan Modifications

Amendments to this document will be provided to the site. Each site is responsible for submitting the amendment to the applicable IRB. EndoStim will submit protocol amendments to the applicable national regulatory authority. Prior approval from the IRB and national regulatory authority will be obtained, when applicable, prior to the implementation of the change except in an emergency situation.

3.9 Investigator Responsibilities

The Principal Investigator is responsible for ensuring that the clinical investigation is conducted according to the Investigator Agreement, this study protocol, the Clinical Trial Agreement, and all applicable federal and local regulations for an Investigational Device Exemption (IDE) study, and any conditions of approval imposed by the reviewing IRB and/or national regulatory authority. The Principal Investigator shall:

- Indicate acceptance of this study protocol in writing by signing the Investigator Signature page of this study protocol and any applicable amendments.
- Conduct this study in compliance with this study protocol and any applicable amendments
- Create and maintain adequate source documentation throughout this study and make source documentation available as requested for monitoring visits or audits
- Ensure the investigational device is used solely by authorized users at the site
- Ensure the investigational device is use in accordance with this study protocol and product labeling
- Refrain from implementing any modifications to this study protocol without agreement from EndoStim, the applicable IRB, and national regulatory authority as required
- Promptly document and explain any deviation from the approved study protocol during the course of this study
- Ensure the investigational site has an adequate staff, resources and training, and document delegations of duties throughout the study
- Ensure study staff members have documented study protocol training
- Ensure adequate facilities exist and are maintained during this study
- Ensure that maintenance and calibration of all equipment relevant to the clinical investigation is appropriately performed and documented as requested
- Ensure the accuracy, completeness, legibility, and timeliness of all data reported to EndoStim (including source documentation as well as eCRFs)
- Maintain accurate and complete device accountability records
- Allow and participate in EndoStim monitoring and auditing activities as requested
- Allow and participate in IRB and national regulatory authority auditing activities
- Ensure all study-related records are retained as required
- Ensure accurate and timely preparation of reports required by applicable regulations

EndoStim retains the right to terminate participating investigational sites for failure to comply with investigator responsibilities, or requirements imposed by applicable IRB and national regulatory authorities.

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Appendix A: Subject Informed Consent Template

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), CS-100

INFORMED CONSENT TEMPLATE

Introduction

Your doctor has explained to you that you have a condition called Gastroesophageal Reflux Disease or GERD and this may be causing you to experience reflux or heartburn. Symptoms are often caused by a weak valve, or sphincter, between the esophagus and the stomach. This structure is called the lower esophageal sphincter or LES. Normally, when liquid and food pass through the esophagus, it opens to allow food and drink to enter the stomach. After passing, the valve closes. When the sphincter is weakened, it can lead to backflow of stomach contents and acid into the esophagus, causing symptoms such as heartburn and regurgitation (Figure 1 and 2).

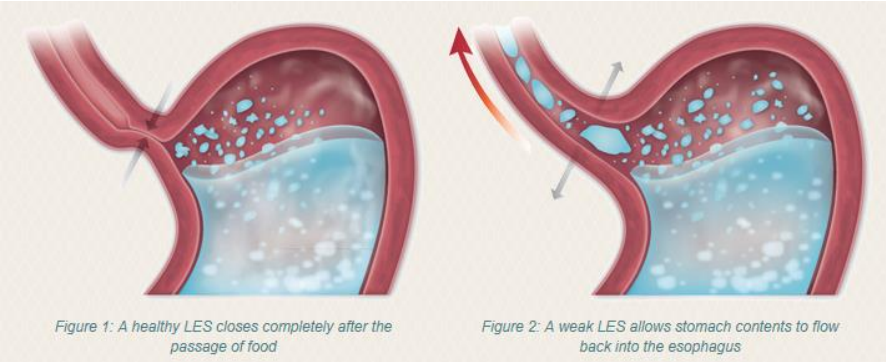


Figure 1 and 2. Lower Esophageal Sphincter

Chronic esophageal reflux can lead to esophageal damage, a pre-cancerous condition called Barrett's Esophagus, and ultimately esophageal cancer. The current medical treatment for chronic reflux is often lifetime use of acid-blocking medication known as proton pump inhibitors. These medications control acid production, but do not target the weak esophageal sphincter muscle. Many patients continue to experience symptoms despite taking medications, often after meals or at night. For more severe cases, surgery may be recommended.

Your doctor is participating in a clinical research study involving the EndoStim Lower Esophageal Sphincter (LES) Stimulation System, which is a new medical device that has been designed to apply tiny electrical pulses to stimulate the lower esophageal sphincter muscle. The electrical stimulation of the LES muscle is intended to restore the function of the LES thereby restoring the barrier between the stomach and esophagus. The EndoStim LES Stimulation System is investigational, which means it is not yet approved to be available to the general public.

You are being offered to consider voluntary participation in a research study of this device sponsored by EndoStim Inc., the manufacturer of the device. It is estimated that approximately 400 subjects from up to 30 centers in and outside of the United States will participate in this research study. Before you decide to participate, you are asked to read this information and ask your doctor any questions you may have about the study and the EndoStim device. You may also ask your doctor questions at any time throughout the duration of this study.

A description of this clinical trial will be available on http://www.clinicaltrials.gov as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Voluntary Participation

Your participation in this study is voluntary. If you do decide to participate, you may quit the study at any time without giving a reason. Just tell your doctor you do not wish to continue your participation. If you leave the study before the final regular scheduled visit, you may be asked by the study doctor to make a final visit. Should you withdraw, it is recommended you continue to see your physician. There will be no penalty or loss of benefits to which you are otherwise entitled if you decide not to continue with the study. Your doctor or the sponsor of the study (EndoStim, Inc.) may also stop your participation in the study at any time, without your consent, due to medical conditions or other factors that affect your study eligibility. Whether you participate in this research study or not, your doctor will continue to make every effort to improve your GERD using standard treatment and this study will not change the availability of these treatments. If you decide to participate, after reading the following information, you must sign and date the last page of this consent form. If you do not sign this form, you will continue to receive care, but not as part of this research study.

Study Purpose

The objective of this study is to investigate if electrical stimulation delivered to your LES is safe and will improve LES muscle tone which, in turn, could improve GERD symptoms.

Parts of the EndoStim LES Stimulation System

The EndoStim LES Stimulation System consists of a stimulator, a small implantable medical device similar to a pacemaker, and implantable leads or electrical wires which deliver stimulations to the LES (Figure 3). The stimulator and leads are implanted within the body.

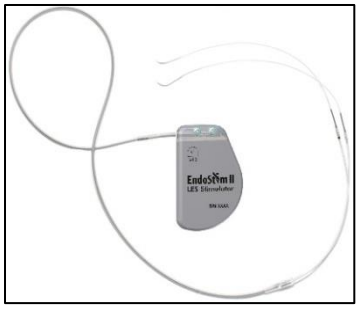


Figure 3. EndoStim Stimulator and Lead

The EndoStim LES Stimulation System also consists of a programmer and hand-held wand (Figure 4) placed directly over the skin in the region where the stimulator is implanted. The programmer is used in the doctor's office by medical personnel to communicate wirelessly with the stimulator using special software installed on a computer. This wireless communication allows your doctor to obtain information about how the device is working and to control the function of the stimulator.

Figure 4. Tablet PC with EndoStim Programmer Software and the Programmer Wand

Study Requirements

If you agree to participate in this study, you will receive medical care and have the following scheduled study activities and follow-up visits:

- Screening and baseline visits
- Implant procedure with a hospital stay (usually go home same day)
- Follow-up office visits after the procedure at 2 weeks, 1, 3, 6, 9, and 12 months. There may also be office visits at 7, 15 and 18 months.
- Follow-up phone interviews after the procedure at 2 and4 months. There may also be phone calls at 8, 10, 18 and/or 24 months.
- Annual follow-up office visits until the study is completed

Attachment A contains a study visit flow chart for your reference.

The procedures that are required as part of the study are described below. Stimulation of the LES and the procedure to implant the device are considered Investigational. None of the other procedures required as part of the study are experimental.

Screening and Baseline Visits

After you give your consent to participate in the study by signing this form, you will have assessments and tests performed and data collected to determine if you meet requirements to participate in the study.

At your first visit, please bring a list of all medications you are currently taking including drug name, pill size, dose, and reason for taking the medication. Your doctor will review your medical history, medication use, and ask you to complete questionnaires to assess your GERD condition. Your doctor will perform a physical examination, electrocardiogram to assess heart function, and laboratory tests on your blood.

The function of your LES may also be assessed using tests called endoscopy, manometry and pH testing, which are often used in clinical practice to evaluate GERD and you may have experienced these tests in the past. Endoscopy involves the use of an endoscope to look inside the esophagus. Esophageal manometry measures the strength and muscle coordination of your esophagus when you swallow and the esophageal pH testing measures the amount of acid in your esophagus over a 48 hour period.

For the endoscopy test, you will be given a sedative and the doctor will pass a flexible tube through your mouth and along the back of the throat and down to the esophagus. The tube has a tiny camera at the end that allows the doctor examine the surface of the esophagus.

For the pH test, the doctor will place a tiny probe in the lower esophagus. The probe transmits this information wirelessly to the patient receiver/monitor. After about 48 hours, you will return the patient receiver/monitor and your doctor will review the pH data.

During the manometry test, a tube is passed through your nose, along the back of the throat, down the esophagus and into the stomach. The tube does not interfere with your breathing. The tube is connected to a machine that records the contractions of the esophageal muscles on a graph. You will be asked to not eat or drink anything eight hours prior to the manometry test. A topical anesthetic (numbing medication) may be applied to your nose to make the passage of the tube more comfortable. If you underwent manometry testing within the last 6 months prior to starting participation in this study, please tell your study doctor because, in some cases, the results of the prior test could be used for this study and you then would not need to repeat it.

If, at any time during the study (in the opinion of your physician), test results are compromised due to noncompliance or equipment malfunction, the relevant test(s) may be repeated.

For 14 days prior to the Baseline Visit, you will be asked to stop taking acid suppressive therapy (PPIs and H2 blockers) and remain off the medications until after completion of the Baseline Visit. While you are off these medications, you will be permitted to use antacids on an as-needed basis to control your GERD symptoms. The antacids that are allowed in the study are Gelusil® and Gaviscon®. This will be provided to you at no cost. For at least 14 days prior to stopping acid suppressive therapy and through the off-acid suppressive therapy period, you will be asked to keep a diary to track your typical medication use and your GERD symptoms. If you are not able to complete the subject diary or stop taking acid suppressive therapy, you may not qualify for participation in this study. During the Baseline Visit, your GERD condition off acid suppressive therapy will be assessed.

After you complete the Baseline Visit, you will be required to go back on PPIs for at least 7 days. Then you will be required to repeat one of the GERD questionnaires you completed at your first Screening visit. You will be able to remain on PPIs until the two-week post-implant follow-up visit.

If you are a female of child-bearing potential, you must be on a reliable form of birth control. Urine pregnancy tests will be performed at the baseline or implant visit.

At the end of the screening and baseline assessments, your doctor will review the information you collected at home as well as the results of the tests. If the test results do not meet study requirements, your participation in the study will end and you will receive standard care as decided upon by your doctor. If you meet study requirements assessed up until now, you will be scheduled and return for the implant procedure. In preparation for the procedure, your doctor may ask you to undergo pre-procedure tests, such as blood tests or a physical examination, as required by the hospital's procedures.

Implant Procedure

On the day of your implant procedure, you will be admitted to the hospital and under the hospital's standard pre-procedure activities. You will be given a general anesthetic. During the laparoscopic study procedure, the study doctor will attach the EndoStim stimulation lead to the lower part of your esophagus. The lead is brought out into a small pocket located under the abdominal skin and connected to the stimulation device (Figure 5). The wound will be then closed and dressed appropriately per standard protocol and a compression bandage will be applied on the wound. The procedure lasts about 40 to 90 minutes. Video recordings of the device implant

procedure may be taken and provided to EndoStim for the purpose of confirming device placement; however, your identity will not be disclosed.

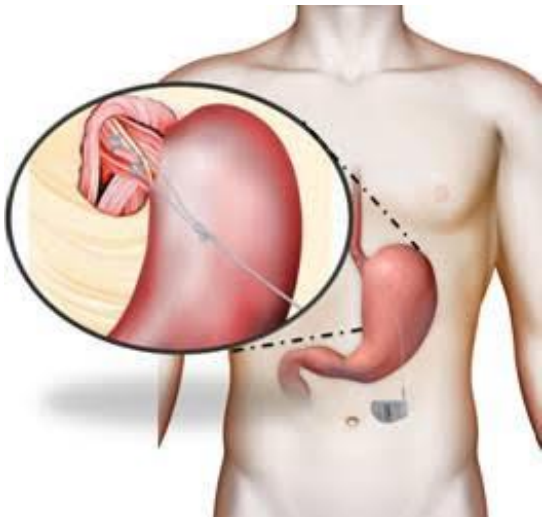


Figure 5. Implanted EndoStim LES Stimulation System

After surgery, you may stay in the hospital until you recover and will usually go home the same day. Once you have recovered from the surgery, the device will be checked to ensure it is functioning properly. Once the doctor determines it is safe for you to go home, you will be discharged from the hospital.

The following diet instructions are recommended:

STAGE 1: CLEAR LIQUID DIET - Night of Surgery

STAGE 2: SOFT DIET - Morning after surgery. Continue at this stage for 3-7 days after surgery or as tolerated

STAGE 3: Start TRANSITION TO REGULAR DIET - About 3-7 days after surgery

STAGE 4: Achieve REGULAR DIET - 3 to 6 weeks after surgery

Two-Week Post-Implant Follow-Up Visit

About two weeks after the implant procedure, you will return the office for an assessment of the implant site to make sure that it has healed properly, a review of your symptoms and medication use, and an evaluation of device function. If your device is functioning properly and you still meet the requirements for being included in this study, you will be randomized to (equal chance of being assigned) to early stimulation treatment [Treatment Group] or delayed stimulation treatment [Control Group] for 6 months. Being randomly assigned happens by chance, much like the result of flipping a coin.

For the results of this study to be valid, you will not be told which group you belong to and will not know this information until after the 6-month follow-up visit. The doctor will also not know which group you are assigned to. This is called “blinding” a study. The purpose of this blinding is to make the reporting of any potential benefits or risks associated with the therapy to be completely unbiased by you or your doctor. If at any point in the trial, if required for your health or safety, your doctor can request the results of the blinding to be revealed.

All patients will undergo device evaluation and programming session steps, but if you are assigned to the control group, no therapy will be given. You will be asked to stop use of GERD medications, but may continue to take

Gelusil or Gaviscon (antacids). If Gelusil or Gaviscon do not reduce your symptoms, you will be given rescue medication to help improve your GERD symptoms. Continue to use the compression bandage for 30 days after the implant procedure.

Follow-Up Visits

You will be asked to return to the study doctor's office for evaluation at 1, 3, and 6 months. You will also be asked to participate in follow-up phone interviews after the procedure at 2 and 4 months. Your doctor will assess the implant site to make sure that it has healed properly, review your symptoms and medication use, complete a physical exam and evaluate the function of your device. Your doctor will ask you to complete questionnaires to assess your GERD condition. Device settings may be changed according to the protocol. You will be asked to keep a diary to track your medication use and symptoms while you are participating in the study. Your doctor will provide you with standard diet and lifestyle instructions and discuss the importance of following these guidelines.

At the 3-month visit after your implant procedure, in addition to the assessments noted above, you will be asked to undergo pH monitoring. You may undergo an endoscopy as part of the pH test. You will be sedated during the endoscopy.

At the 6-month visit after your implant procedure, in addition to the items noted above, you will also be asked to complete tests called endoscopy (with sedation), manometry and pH monitoring, and laboratory tests of your blood (similar to the baseline tests). If you are a female of child-bearing potential, urine pregnancy tests will be performed. Also at this visit, you will be told whether or not you have been receiving stimulation treatment.

- If you had been receiving treatment, you will continue to receive treatment for the remainder of the study and will be asked to return for 9- and 12-month office visits. A follow-up phone interview will also be completed at 18 months.

At the 9, 15 and 18 month visits, in addition to the assessments noted above, you may be asked to undergo pH monitoring and bloodwork. You may be asked to undergo an endoscopy (with sedation).

If you had not been receiving treatment, your device will be turned on and you will receive treatment for the remainder of the study. You will be asked to return to the study doctor's office for evaluation at 7, 9, and 12 months, and you will also be asked to participate in follow-up phone interviews at 8 and 10 months – these activities are the same as those activities you just completed for the first 6 months after your implant procedure, but this time, your device will be turned on and you will have the opportunity to receive stimulation therapy and have this therapy modified according to the protocol. You will be asked to return to the study doctor's office at 15 and 18 months. A follow-up phone interview will also be completed at 24 months.

At 12 months you will be asked to undergo pH monitoring, endoscopy (with sedation) and blood work; if you were randomized to the control group you will also be asked to undergo manometry.

Each year thereafter, at the anniversary of starting your stimulation therapy, through 5 years after stimulation therapy was turned on; you will be asked to return to the doctor's office for follow-up evaluations. Your doctor will assess the implant site to make sure that it has healed properly, review your symptoms and medication use, complete a physical exam and evaluate the function of your device. Your doctor will ask you to complete questionnaires to assess your GERD condition. Device settings may be changed to suit your needs. You will be asked to keep a diary to track your medication use and symptoms for at least 10 days prior to each annual visit.

Your doctor will provide you with standard diet and lifestyle instructions and discuss the importance of following these guidelines.

Please keep all appointments with your doctor. Inform your doctor if you move or change addresses.

Study Completion

At the end of the study, you may choose to continue stimulation therapy and be followed per your doctor's recommendations. You may also discuss with your doctor whether the implanted lead and/or stimulator should be turned off or removed in part or completely. The decision will be based on your doctor's opinion and your evaluation of the extent to which you have benefitted from the device. If, at the discretion of the study doctor, a decision has been made to remove the device, a date within 3 months will be set for your admission into the hospital. Once you have recovered, the study doctor will discharge you home. You will be asked to return to the doctor's office approximately one week later for a follow-up evaluation. Your doctor will evaluate the wound and remove the suture, assess any adverse events, and complete a physical exam. Approximately one year after removal of the device, you will be contacted by phone to for a routine follow-up call to assess any potential adverse events and to complete questionnaires to assess your GERD condition and medication use.. This will complete your participation in the study.

If you or your doctor decides to remove the implanted lead and/or stimulator before the study ends, the device will be removed as described above, and you will be asked to participate in the additional follow-up visits described above at one week and one year post-explant. The costs of the device removal will be covered by EndoStim in case the device will be removed within the study period or within 3 months after the study ends.

Duration of Participation

Your participation in the study is expected to last up to 5 years. It is possible the study could be closed before you have reached the 5-year annual follow-up visit. This study will collect data from your past medical history including past treatments for GERD, GERD-related medication use and use of healthcare resources.

Discomforts and Risks

There are risks, discomforts, and inconveniences associated with any research study that you should consider before deciding to participate in this study. Precautions will be taken to ensure that side effects, should they occur, will be addressed. Side effects may last only a short time. However, sometimes side effects can be serious, long lasting or permanent. Tell your doctor if you have any problems. Your doctor will discuss the best way of managing any side effects with you.

Having blood taken may cause some discomfort or bruising. Sometimes, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which blood is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can be easily treated.

Although manometry and pH testing is commonly used to assess GERD, there are possible risks. You may experience pain or discomfort when the manometry or pH tube is placed in your esophagus. Your doctor will give you a local anesthetic to prevent any pain or discomfort. You may also experience retching or vomiting which could increase your risk of aspirating a food particle into your 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, you will fast prior to manometry tube placement. Risks associated with endoscopy include infection, bleeding or tearing (perforation) of tissue in the esophagus, allergic reaction to the medication

used for the procedure, or aspiration of contents into the lungs. This may require the use of antibiotics, hospitalization and sometimes a surgery to repair it.

Possible risks associated with the laparoscopic procedure include: unstable blood pressure, vertigo (dizziness), hematoma (collection of blood outside a blood vessel), seroma (collection of fluid in the body), injury to organs, blood vessels or other structures, internal bleeding, bleeding from the incisions, blood clot, nerve damage, tissue perforation, abrasion or erosion, injury to organs within the abdominal cavity, wound separation, intravenous site complications, partial or complete blockage of the bowel, inflammation, infection, fever, adhesions (bands of scar tissue inside the body), pneumonia, cardiac arrhythmia (irregular heartbeats), cardiopulmonary depression (slowed breathing), incisional hernia, sleep problems (insomnia), excess salivation, hiccups, dysphasia (difficulty swallowing), bloating, belching, dyspepsia (indigestion), early satiety (feeling full after eating) or eating less, worsening pre-existing psychiatric illness, pain or discomfort related to the surgical procedure. Rarely, the gas that is passed to the abdomen can cause heart, lung or chest complications. Some of these events, if they were to occur, may require medicines, fluid replacement, blood transfusion (replacement), and/or another surgery to treat the event. In some cases, hospitalization may be required for further evaluation and treatment. Death as a result of this procedure is possible. **Possible anesthesia risks** include but are not limited to nausea, vomiting, fever, hypoxia (reduction in oxygen to tissues), pneumonia, adverse drug reactions, urine retention, clumsiness, drowsiness, blurred vision, and death.

Right after the procedure, subjects may experience bloating or bruising and/or pain around the incisions, shoulder pain, sore throat, and cramping in the stomach. In some subjects, healing of the wound may be abnormal and the wound can be thickened and red and the scar may be painful.

Potential adverse effects/events associated with the implantation of the EndoStim IPG and lead include, but are not limited to, the following: bleeding; pain or discomfort; hematoma (collection of blood outside a blood vessel); seroma (collection of fluid in the body); wound separation; incisional hernia; infection; inflammation; fever; dysphagia (difficulty swallowing); blood clot; partial or complete blockage of the bowel; tissue perforation, abrasion, or erosion; injury to organs within the abdominal cavity; pneumonia; cardiac arrhythmia (irregular heartbeats); cardiopulmonary depression (slowed breathing); and death.

Adverse effects that could be associated with the EndoStim System include, but are not limited to, the following: lead/electrode dislodgement (movement out of position); lead erosion or perforation (tear) into the esophagus, stomach, or intestine; stimulator migration (movement) in the subcutaneous space; stimulator erosion through the skin; diaphragmatic stimulation (stimulation of the diaphragm); stimulation of abdominal muscle; irritation, pain, and/or inflammatory response to the stimulator and/or the lead; allergic reaction to materials; worsening of GERD symptoms or test results; irritable bowel syndrome or dyspepsia (indigestion); flatulence; nausea; excess salivation; bloating; belching; inability to belch or vomit; food impaction; regurgitation of food or mucus or vomiting; globus sensation; early satiety (feeling full after eating), eating less, or weight loss; dysphagia (difficulty swallowing); odynophagia (painful swallowing); hematoma (collection of blood outside a blood vessel); infection; cardiac arrhythmia (irregular heartbeats); worsening pre-existing psychiatric illness; and discomfort.

Your stimulator has an internal battery that is sealed and cannot be replaced. Batteries do not run indefinitely, and the one inside your stimulator is not rechargeable. Stimulation therapy stops when the battery in the stimulator is completely discharged. Talk to your doctor about the battery life. When it is time to replace the battery, your doctor will remove the stimulator and replace it with a new one, which requires another minor medical procedure that is usually performed under a local anesthetic or procedural sedation.

There is a potential that any system component could malfunction (e.g., software bug), become damaged (e.g., lead fracture), or your incision could become infected. System component malfunction or other clinical circumstances (e.g., systemic infection) may require noninvasive corrective actions or possibly even a surgical revision (repositioning, replacement, or removal) of the malfunctioning component(s). Over time, there is a potential for loss of therapeutic effect, even if the system is functioning properly.

Attachment B contains general precautions to be followed with the implanted EndoStim LES Stimulation System. Inform any medical personnel that may be treating you for other conditions that you have an implanted EndoStim LES Stimulation System.

There may be other risks that are not known at this time. Tell your doctor immediately about any new or unusual signs or symptoms.

Women of Child-Bearing Potential

The effects of EndoStim therapy on the unborn child and on the newborn baby are not known. Because of this, you must not participate in the research study if you are pregnant, trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the implant procedure and periodically throughout the study. If you do become pregnant while participating in the study, you should advise your treating doctor immediately.

Potential Benefits

You may receive relief of your GERD symptoms while participating in this study and reduce reliance on GERD medications. Specific benefits are not guaranteed. Nevertheless, the data obtained from this study will help your doctor learn more about your condition. The information gathered from the study will add to the understanding of the treatment options for patients with GERD, and may advance medical science, which may benefit other patients suffering from GERD.

Alternative Treatments

In most cases, patients suffering from heartburn or acid reflux are recommended to modify their lifestyles and take one of many over-the-counter or prescription medications. However, many GERD patients experience symptoms despite daily medications and few will opt to undergo major surgery.

Lifestyle Modification

Some GERD sufferers find relief from dietary and lifestyle modifications, such as avoiding foods that trigger symptoms, eating smaller, more frequent meals, avoiding alcohol, abstaining from reclining within 3 hours of eating, and losing weight.

Medication

Drug therapy has been widely accepted as the solution of choice for less severe patients. Medications like acid reducers, such proton pump inhibitors (PPIs) or H2 blockers, block or reduce stomach acid production and may help relieve heartburn. Medications such as acid neutralizers or antacids neutralize stomach acid which may increase the pH and reduce heartburn symptoms. Some patients take more than one medication, more than one time per day, to relieve GERD symptoms. However, patients on medications may still suffer from reflux of weakly acidic or non-acidic stomach contents which may cause symptoms such as regurgitation, chest pain, and

sore throat. Often, GERD is treated with lifetime use of antacids and PPIs, but growing concerns about long term safety of these drugs is driving patients and physicians to look for alternate treatment options.

Surgery

For more severe cases, the surgical standard of care is fundoplication, which involves permanently wrapping the top of the stomach around the esophagus (Figure 6).

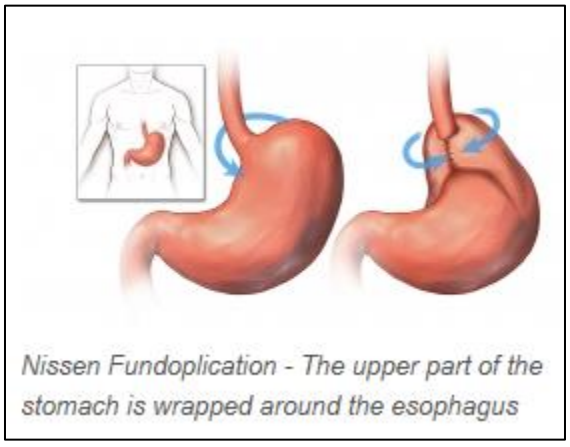


Figure 6. Nissen Fundoplication

Traditionally, surgery has been reserved for a very small number of patients who do not respond to drug therapy. Nissen Fundoplication results in irreversible changes in anatomy and potentially serious side effects. Fundoplication is also an invasive procedure and may eventually fail over time. Many patients who undergo fundoplication return to taking acid reducing and/or neutralizing medications. Other surgical techniques and devices have become available over the past decade, but those techniques also constrain the esophagus, resulting in symptoms such as difficulty swallowing and gas bloat. Your doctor will discuss if any of these treatment options are a suitable alternative option for you.

New Findings

You will be informed of any significant new findings that may impact your decision to continue participation in the study.

Confidentiality and Authorization to Use and Disclose Information for Research Purposes

Your research and hospital records are confidential. Neither your name nor other personally identifying information will be used in any publication about this study. Representatives from the FDA, the sponsor, the sponsor's agents or other authorized agencies may inspect your records. By signing this consent form, you authorize us to use the clinical information in your treatment records for reporting the results of this study to the FDA, the sponsor and to the scientific community. Every effort will be taken to keep your name and other identifying information confidential.

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctors must get your authorization (permission) to use or give out any health information that might identify you.

Your records of being in this study will be kept private except when ordered by law. The following people will have access to your study records:

- The study doctors or study staff
- Sponsor company or research institution [including monitor(s) and auditor(s)]
- The United States Food and Drug Administration (FDA)
- Other country, state or federal regulatory agencies
- Institutional Review Board (IRB)

The IRB and accrediting agencies may inspect and copy your records, which may have your name on them. Therefore, total confidentiality cannot be guaranteed. If the study results are presented at meetings or printed in publications, your name will not be used.

WHAT INFORMATION MAY BE USED AND GIVEN TO OTHERS?

If you choose to be in this study, the study doctors will get personal information about you. The study doctors may also get information about your health including:

- Past and present medical records
- Study records
- Records about phone calls made as part of this study
- Information that can be used to contact you
- Records about your study visits
- Information obtained during this study
- Records about the study device

WHO MAY USE AND GIVE OUT INFORMATION ABOUT YOU?

Information about your health may be used and given to others by the study doctors and staff. They might see the research information during and after the study. You will be in the study for up to 5 ½ years; the information may also be used after that time.

WHY WILL THIS INFORMATION BE USED AND/OR GIVEN TO OTHERS?

Information about your health may be used and given to others to carry out the study. The sponsor will analyze the results of the study. In addition, people from the sponsor and its consultants will be visiting your study doctors' offices. They will follow how the study is done, and they will be reviewing your information for this purpose. The sponsor may use this information in its research, development, quality improvement, and other business processes, including submission to government agencies. For example, the information may be given to the FDA. This is done so the sponsor can receive marketing approval for new products resulting from this study or for future products. The information may also be used to meet the reporting requirements of government agencies. The

results of this study may be published in scientific journals or presented at medical meetings, but you will not be identified. The information may be reviewed by the IRB.

WHAT IF I DECIDE NOT TO GIVE PERMISSION TO USE AND GIVE OUT MY HEALTH INFORMATION?

By signing this consent form, you are giving permission to use and give out the health information listed above for the reasons described above. If you refuse to give permission, you will not be able to be in this study.

MAY I REVIEW OR COPY THE INFORMATION OBTAINED FROM ME OR CREATED ABOUT ME?

You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your study-specific information until after the study is over.

MAY I WITHDRAW OR REVOKE (CANCEL) MY PERMISSION?

Yes, but this permission will not stop automatically. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctors. If you withdraw your permission, you will not be able to continue in this study. Any of your health information that has already been disclosed will continue to be available for the study and for reporting to government agencies.

IS MY HEALTH INFORMATION PROTECTED AFTER IT HAS BEEN GIVEN TO OTHERS?

If you give permission to give your identifiable health information to a person or a business, the information may no longer be protected. There is a risk that your information will be given to others without your permission.

Costs and Compensation

The institution where the study is being conducted is being compensated by the EndoStim to perform this research study. There will be no compensation to you for participating in this study; however reimbursement of reasonable costs for travel as needed for required study visits to your research document may be available.

Certain procedures and treatments that you receive in the course of the study are routine, that is, they are services and care you would receive even if you were not participating in the clinical study. These procedures and services will be covered by your insurance and you will be expected to pay any co-insurance, copayment and deductible fees that you would normally have to pay. In addition, your insurer may agree to cover the experimental device and procedure. If that is the case, you may be responsible for co-payments and deductibles, as noted above. You will not be asked to pay for tests and procedures that are being performed strictly for the purpose of evaluating the study device that are not standard of care.

In the event you become injured as a result of participation in this study, medical care will be available. You are expected to pay for such treatment or seek reimbursement by your health insurance provider. EndoStim will

cover the costs of reasonable and necessary treatment of study-related injuries that are not standard of care while you are in the study. Payment for such case does not limit or waive any rights that you may have against EndoStim, and EndoStim does not admit fault by offering payment. EndoStim is not responsible for problems caused by your failure to follow study instructions, including attending all follow-up visits. If you think you have suffered a research-related injury, you must contact your doctor right away.

Study Contacts

If at any time you have questions regarding the research or your participation, you should contact the investigator who must answer all questions to the best of his/her knowledge.

Name:

Address:

Contact Information:

If at any time you have comments regarding the conduct of this research or questions about your rights as a research subject, you may contact the ethics committee overseeing the study at:

Name:

Address:

Contact Information:

Consent

I have read all of the above information in this consent and authorization form. I have had the opportunity to ask questions and have received answers concerning areas I did not understand, and willingly give my consent to participate in this study. I authorized the use and disclosure of my health information to the parties listed in the Authorization section of this form for the purpose described above. By signing this form, I have not waived any of the legal rights which I otherwise would have as a participant in a research study.

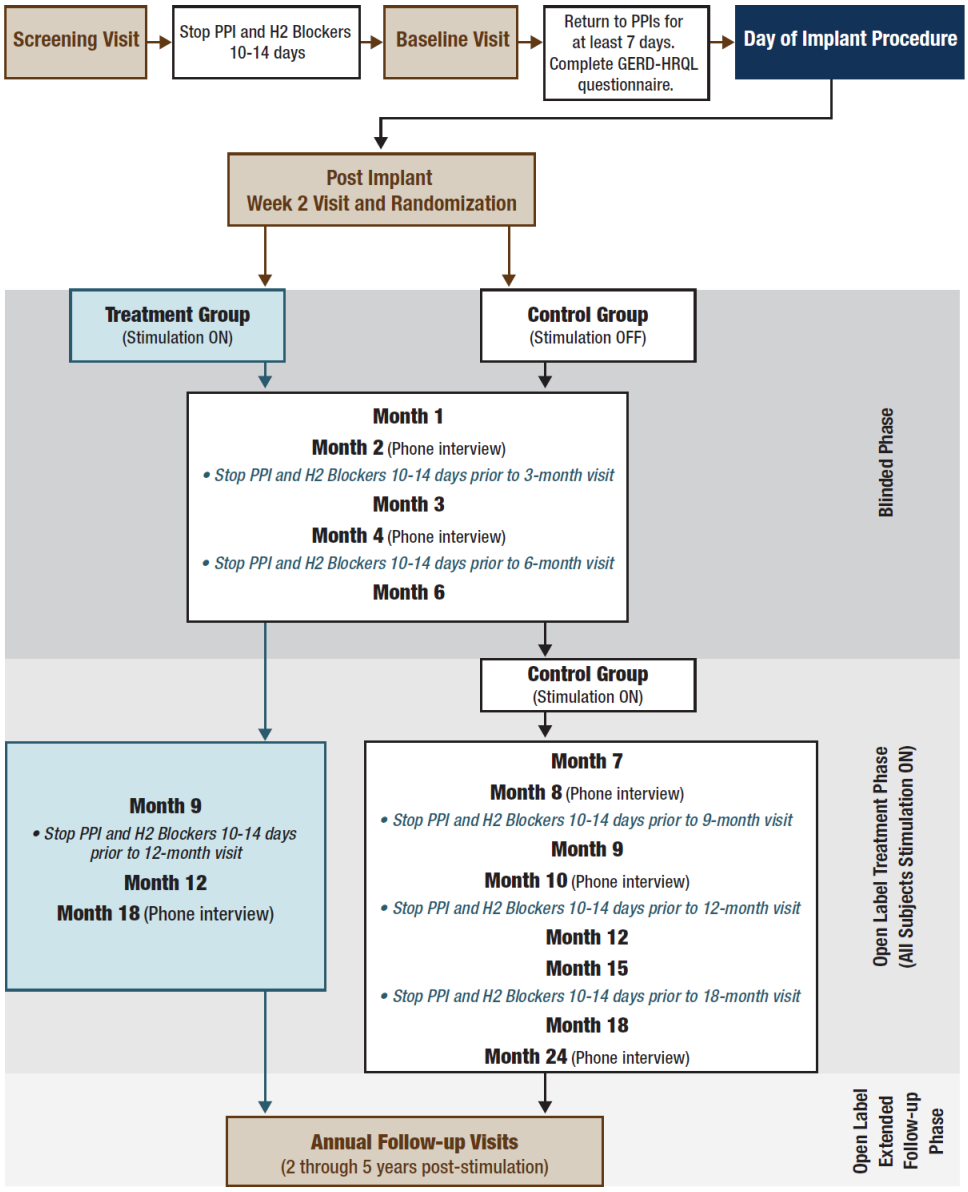
Patient's Name (printed)	Signature	Date

Subject ID Number: 100- __ __ __ - __ __ __

I, the undersigned, certify that to the best of my knowledge, that participant signing informed consent has had the study fully and carefully explained and expresses understanding of the nature, risks, and benefits of participation in the clinical research study.		
Name of Investigator or Person Delegated by the Principle Investigator (printed)	Signature	Date

Impartial Witness Name (printed)	Signature	Date

Attachment A. Study Visit Flow Chart



Attachment B. General Precautions Associated with the Implanted EndoStim Stimulator and Lead

Activities—Avoid activities that may put undue stress on the implanted components of the EndoStim System. Activities that include sudden, excessive, or repetitive bending, twisting, bouncing, or stretching can cause component fracture or dislodgement. Component fracture or dislodgement can result in a cessation of stimulation, intermittent stimulation, stimulation at the fracture site, and additional surgery to replace or reposition a component.

Twiddler's syndrome—Avoid manipulating or rubbing the implanted components of the EndoStim System, which can cause component damage, skin erosion, or stimulation at the implant site.

Scuba diving—Do not dive below 7.4 meters (24 feet) of water or enter hyperbaric chambers above 1.5 atmospheres absolute (ATA) or 150 kPa (21.8 pounds per square inch absolute). Pressures below 7.4 meters (24 feet) of water (or above 1.5 ATA) could damage the EndoStim System. Before diving or using a hyperbaric chamber, discuss the effects of high pressure with your doctor.

Home appliances—Home and commercial microwave ovens in good condition, and used as intended, will not affect the EndoStim IPG. Even a defective oven that exposes the stimulator to direct microwave energy may not damage the unit itself. Ovens using electromagnetic induction can cause the device to go into magnet mode (disable stimulation therapy output). Be advised of the possibility of interference from some electric razors, electric power tools and electrical ignition systems, including those used on gasoline-powered devices. In general, patients who have an stimulator may operate gasoline-powered devices if protective hoods, shrouds, and other shielding remain in place.

Anti-theft systems/Security screening devices—Use care when approaching theft detectors and security screening devices (such as those found in airports, libraries, and some department stores) as these devices may cause temporary interference or permanently reset the device.

If possible, request to bypass these devices. Show the security personnel your patient identification card for the EndoStim System and request a manual search. Security personnel may use a handheld security wand, so ask the security personnel not to hold the security wand near the stimulator for any longer than is absolutely necessary. You may want to ask for another form of personal search.

If you must pass through the theft detector or security screening device, approach the center of the device and walk through normally. Do not linger near, or lean on, the screening device.

Industrial machinery—Exercise care or avoid the following equipment or environments:

- Antenna of citizen band (CB) radio or ham radio
- Electric arc welding equipment
- Resistance welders
- Electric induction heaters used in industry to bend plastic
- Electric steel furnaces
- High voltage (safe if outside the fenced area)
- Television and radio transmitting towers (safe if outside the fenced area)
- Microwave communication transmitters (safe if outside the fenced area)
- Linear power amplifiers
- High power amateur transmitters
- Perfusion systems
- Magnets or other equipment that generate strong magnetic fields
- Magnetic degaussers

Portable devices—Cellular and wifi-enabled devices can interfere with the operation of the EndoStim System. Potential effects may result from either the radio frequency emitted by these devices or the magnet within the device speakers. These effects may include inhibition or inappropriate triggering of electrical stimulation delivery when the phone is in close proximity (within 25 cm) to the stimulator or lead. Hold cellular phones to the ear opposite the side of the implanted stimulator. Do not carry the cellular phone in a breast pocket or on a belt over or within 25 cm of the implanted stimulator because some cellular phones emit signals when they are turned on though not in use.

Environmental hazards—Do not use any other electrical equipment adjacent to the EndoStim System. If the components cannot be kept separate, then ask your doctor to monitor the system to assure normal operation. Portable and mobile RF (radio frequency) equipment can interfere with the normal operation of the EndoStim System. The portable and mobile RF equipment should be considered in any situation where the EndoStim System devices are not acting as expected. Other equipment may interfere with these devices, even if that equipment complies with CISPR emission limits. All the components of the EndoStim System can be affected by

magnetic, electrical, and electromagnetic signals of sufficient strength. On rare occasions, interfering signals could inhibit electrical stimulation delivery or, alternatively, trigger inappropriate delivery of electrical stimulation signals. In addition, certain sources can couple sufficient energy into the stimulator to damage the circuitry of the stimulator and/or LES tissue adjacent to the electrodes. Because of the diversity of potential causes of electromagnetic interference, EndoStim cannot characterize and describe within this manual the effects of all potential sources of interference.

Warning: Be cautious when in the vicinity of equipment that generates electrical or magnetic fields, and seek medical advice before entering an area posted with a warning for pacemaker patients (or other medical implantable devices).

Transcutaneous Electrical Stimulator (TENS)—Inform any medical personnel that may be treating you for other conditions that you cannot have a TENS procedure in the abdominal region. If you have a TENS device and you feel that the TENS unit may be interfering with the stimulator, talk with your doctor.

Electrocautery—If you need any surgical procedure where the surgeon may use electrocautery, inform the surgical team that you have the EndoStim system. The surgical use of electrocautery can cause the stimulator to become inactive and possibly lose data. Electrocautery may damage the stimulator and lead. Application of electrocautery close to a stimulator can also cause damage to the LES tissue, possibly producing burns.

RF ablation—RF Ablation can cause the stimulator to revert to its "DOWN" mode, with possible loss of data. If sufficient energy is coupled into the system, the unit may be damaged. Application of RF ablation in close proximity to the electrodes of an implanted IPG can also cause a direct coupling of radio-frequency energy through the leads and electrodes to the LES tissue, possibly producing burns.

Defibrillation—If you need to have an implanted cardiac device, the physicians involved in both treatments should discuss the possible interactions between the implanted devices. Cardiac defibrillation procedures can damage any implanted active medical device. In addition, the defibrillation current can cause damage to LES tissue next to the electrodes and/or to tissue surrounding the IPG. The defibrillation current may also cause the stimulator to revert to its DOWN mode, with possible loss of data. If sufficient energy enters the system, the unit may be damaged. If an external defibrillation unit has been used on you while implanted with the EndoStim System, contact your physician to assess the IPG.

Therapeutic radiation—Therapeutic equipment that produces ionizing radiation, such as linear accelerators and cobalt machines used in cancer treatment, can damage the type of circuitry used in most active implantable medical devices. Damage to the stimulator may not be immediately detected.

Therapeutic magnets—Therapeutic magnets (e.g., magnetic mattresses, blankets, wrist wraps, elbow wraps, etc.), can inadvertently turn the device OFF for a period of 24-48 hours. Place therapeutic magnets at least 10 inches (25 cm) away from your stimulator. Magnetic fields of less than 10 Gauss will generally not affect the stimulator.

Magnetic Resonance Imaging (MRI)—Inform any medical personnel, such as the MRI technologist and/or radiologist that may be treating you for other conditions that there is conditional MRI approval for this device. Your EndoStim physician must be contacted prior to an MRI to be sure the required precautions are followed .

Medical diathermy—Inform any medical personnel that may be treating you for other conditions that you cannot have diathermy treatments. Diathermy treatments can expose you to strong magnetic fields, which may interfere with your stimulator or cause tissue damage.

Lithotripsy—Avoid exposure to lithotripsy. Directly exposing a stimulator to lithotripsy shock waves can cause damage to the device. If the implant site is outside of the shock-wave path, no clear contraindication to the use of lithotripsy can be established.

Therapeutic and diagnostic ultrasound—Direct exposure of a stimulator to diagnostic ultrasound can cause damage. Moreover, the stimulator may inadvertently concentrate the ultrasonic field and cause you harm.

Appendix B: Subject Questionnaires & Other Patient-Facing Materials

The following questionnaires will be used under this protocol. These questionnaires are controlled under EndoStim's Quality System and will be provided in paper format to clinical sites as needed throughout the study.

- Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) Heartburn Questionnaire (Document CA-14)
  - Under protocol amendment F, the GERD-HRQL was updated to the 11-question version, which added one additional question (question #9) regarding bloating (Velanovich V. The development of the GERD-HRQL symptom severity instrument. Diseases of the Esophagus (2007) 20, 130–134). Question #9 will not be included in the score that is used to determine eligibility. Further details on the analysis of results from this question will be addressed in the statistical analysis plan.
- Reflux Symptom Index (RSI) (CA-18)
- Pittsburgh Sleep Quality Index (PSQI) (CA-17)
- SF-12 (CA-19)
- Structured GI Symptoms (CA-20)
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP) (CA-21)
- EndoStim Pre-Implant Diary (CA-22)
- EndoStim Post-Implant Diary (CA-23)
- Diet & Lifestyle Modifications (CA-12)
- Healthcare Utilization Questionnaire (CA-15)
- Post-EndoStim Diet Instructions (CA-16)
- Patient Manual (PM-06)
- Patient ID Card (PN 6600)