FDA Executive Summary Memorandum

Prepared for the January 11, 2012, Meeting of the
Gastroenterology and Urology Devices Advisory Panel

P100049
LINX Reflux Management System
Torax

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I. Introduction

The applicant, Torax Medical, Inc., has submitted a premarket approval application (PMA), P100049, to FDA requesting marketing approval\ for the LINX™ Reflux Management System. The LINX device is an implantable device for the treatment of pathologic Gastroesophageal Reflux Disease (GERD) in patients who continue to have chronic GERD symptoms despite anti-reflux therapy.

The clinical trial was conducted under G060172; the sponsor first conducted a feasibility study and then the pivotal study. The PMA for the LINX™ Reflux Management System was submitted as a modular PMA; the PMA is the fourth module and was filed on December 30, 2010.

GERD is one of the most prevalent disorders seen in the practice of gastroenterology and medicine. It is a symptom complex resulting from the refluxing of material, most often gastric acid, into the esophagus. GERD is multifactorial in etiology. Factors which may play varying roles in the development of GERD includes mucosal defense, effectiveness of esophageal clearance of acid (by peristalsis), potency of refluxate, competency of the lower esophageal sphincter (LES)/crural diaphragm, and transient LES relaxations. Diet, medications, body habitus and activity can affect these factors.

Symptoms of GERD are generally thought of as heartburn or regurgitation radiating towards the neck. Dysphagia is also a common symptom. Less frequent or atypical symptoms of GERD include posterior laryngitis, acid-induced asthma, and atypical (non-cardiac) chest pain. GERD can lead to further morbidity in the way of esophagitis, strictures, and Barrett's esophagus.

Diagnosis of GERD is usually made by the patient's symptom complex. Several ancillary tests, however, may give further information regarding the disease. A 24-hour ambulatory pH study can aid in detecting the percentage of time that the esophagus is exposed to acidic fluid or material during an extended period of time and is the most objective test to diagnose GERD. Upper endoscopy is often performed to evaluate for the effects of GERD including esophagitis and Barrett's esophagus. Esophageal manometry may be used to assess the patient's lower esophageal sphincter competency and esophageal clearance abilities.

Patients with GERD are first advised to make dietary and lifestyle changes such as losing weight, eating smaller meals, and avoiding certain types of foods that may trigger symptoms. If a patient does not respond to these measures, a variety of medications are available, including antacid, H_2 receptor blockers, and proton pump inhibitors (PPIs).

If lifestyle changes and medication use fail, patients may be considered for surgical treatment. The primary alternative for GERD patients with incomplete symptomatic response to PPIs is the Nissen fundoplication. This procedure involves the dissection and wrapping of at least a portion of the stomach fundus around the esophagus. Variability in the wrap in terms of circumference, length and tightness, in addition to surgeon skill and experience all contribute to variable outcomes and significant side effects. Surgical therapy is usually reserved for patients that are

poorly responsive or intolerant of medications or for young patients who would otherwise require life-long medical therapy.

Several devices have been marketed for the treatment of GERD. In the 1980s, the Angelchik device (Allergan) was introduced. This was a silicone ring which was surgically placed around the cardia region and tied in place. Problems with erosion into the gastrointestinal lumen, however, led to the decline in use of this device and its withdrawal from the market. In 2002, Enteryx, an injectable bulking agent, was approved for use in patients with GERD symptoms that responded to and required daily therapy with PPIs. In September 2005, Boston Scientific voluntarily recalled all Enteryx products from commercial distribution based on the possibility of an unrecognizable transmural injection into a vital organ.

Other devices used in endoluminal procedures have been used as alternatives to PPIs and fundoplication. The Endoscopic Suturing System (Bard), EsophyX System (Endogastric Solutions) and the Endoscopic Plication System (NDO Surgical Inc) are indicated for the treatment of the symptoms of chronic gastroesophageal reflux disease in patients who require and respond to pharmacological therapy. These devices create a plication of tissue near the gastroesophageal junction adding to the reflux barrier.

Another type of device is the Stretta System. This device delivers radiofrequency energy to the lower esophageal sphincter by way of tiny electrode needles. Gradual scarring causes contraction of the LES region, again adding to the reflux barrier.

This PMA application includes information regarding the feasibility and pivotal IDE trial results, device design, manufacturing data, preclinical data (including animal study data), reports of prior clinical experience and postmarket approval data collection plans.

II. Regulatory History

The PMA, P100049, has been reviewed by the Office of Device Evaluation, Division of Reproductive, Gastro-Renal and Urological Devices within the Center for Devices and Radiological Health of the Food and Drug Administration. A chronology of the key milestones with respect to this premarket approval application is provided below.

- **September 29, 2006 –** FDA approval of feasibility study under G060172
- **July 25, 2008 –** FDA approval of pivotal study
- **February 24, 2010** – approval of modular review for the LINX Reflux Management System under M090221
- **December 30, 2010** – FDA filed P100049 for the LINX Reflux Management System. The initial submission contained the analysis of the 100-patient pivotal, prospective, multi-center, single-arm study.
- **May 10, 2011** – FDA issued a major deficiency letter that included concerns regarding the long term effects of the device on the subjects enrolled in the study.
- **October 11, 2011 –** applicant submitted response to the questions in the major deficiency letter.

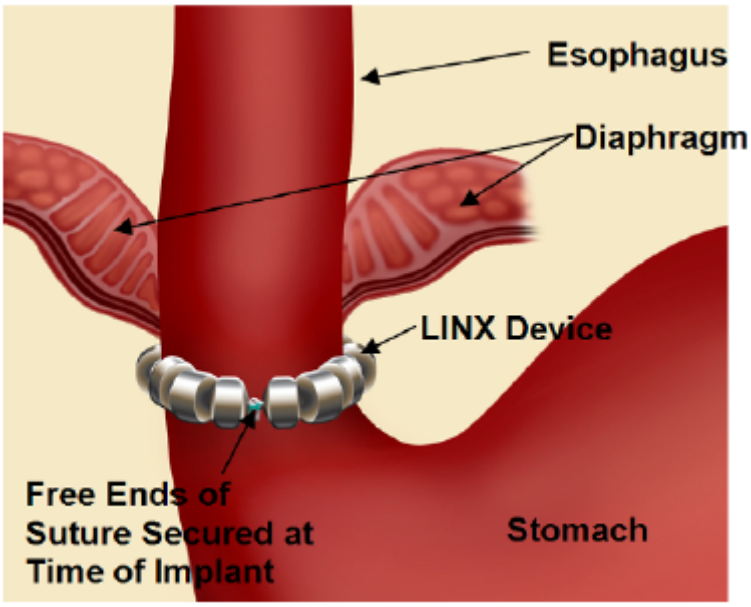
III. Proposed Indications for Use

The Torax LINX™ Reflux Management System is indicated for those subjects diagnosed with pathologic Gastroesophageal Reflux Disease (GERD) as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite anti-reflux therapy.

IV. Device Description

The LINX Reflux Management System is a sterile, single use, surgically placed device used to treat the symptoms associated with gastroesophageal reflux disease (GERD). The device is placed at the area of the lower esophageal sphincter (LES) and is designed to augment a weak LES (Figure 1).

Figure 1: Illustration of the LINX Device on the Esophagus



The LINX Reflux Management System is comprised of two components:

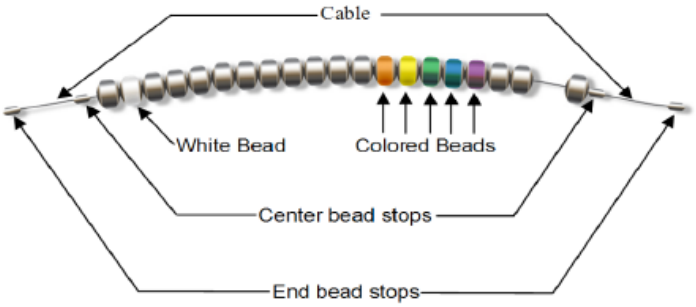
- LINX Reflux Management System Implant
- LINX Reflux Management System Esophagus Sizing Tool (packaged separately)

The LINX device (Figure 2) consists of a series of titanium beads with magnetic cores that are connected with independent titanium wires to form an "annular" shape, when implanted. The attractive force of the magnetic beads is designed to provide additional strength to keep a weak LES when closed. When the patient swallows, the beads slide away from each other on the independent titanium wire "links" to allow esophageal distention as food passes by. The LINX device is available in multiple sizes to accommodate variation in esophagus size. The sizes are denoted by the model number (e.g., LS 12 = 12 bead implant).

Figure 2: LINX Reflux Management System Implant (closed and opened)

The LINX Sizing Tool (Figure 3) is used to determine the appropriate LINX device size. This single use tool is used at the time of implant to assist the physician in choosing an appropriately sized device. Following laparoscopic access to the esophagus, the physician wraps the esophagus sizing tool around the esophagus at the region of the LES. The color coded magnetic beads are then visually aligned around the outer circumference of the esophagus to determine the appropriate sized implant device.

Figure 3: LINX Reflux Management System Esophagus Sizing Tool



BEAD COLOR	ASSOCIATED DEVICE (BEAD LENGTH)
Pre-Orange	10-Bead
Orange	11-Bead
Yellow	12-Bead
Green	13-Bead
Blue	14-Bead
Purple	15-Bead
1st Bead Post-Purple	16-Bead
2nd Bead Post-Purple	17-Bead
3rd Bead Post-Purple	18-Bead

Note: Device size will be rounded to the next higher length in the event the white bead falls between two colored beads on the Esophagus Sizing Tool.

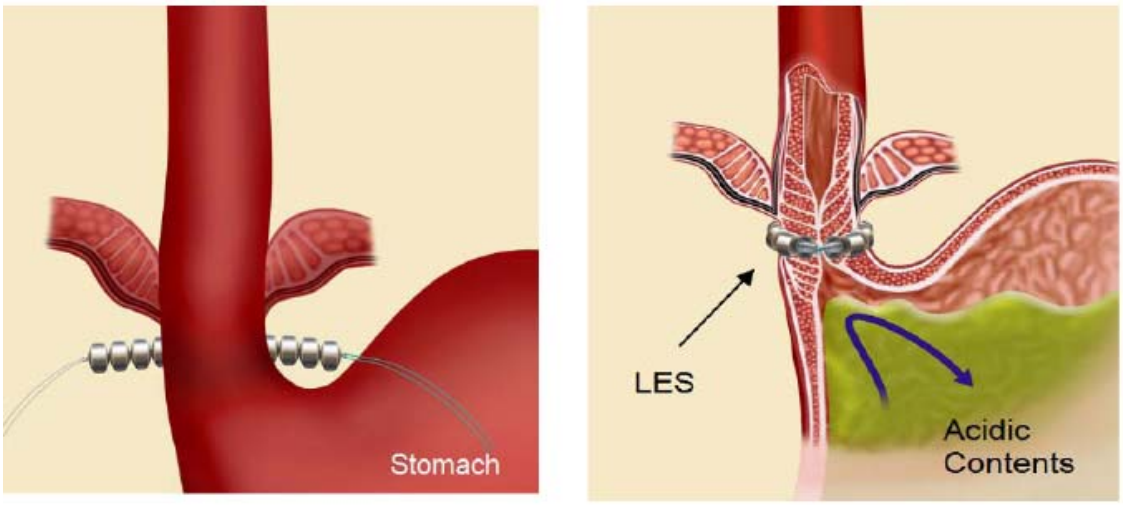
Principles of Operation

The LINX device is used to augment a weak LES and restore the "barrier" function of the LES. The mechanism of action is to augment the sphincter's capacity to resist gastric pressure by the magnetic force of the beads. For abnormal reflux to occur following implantation, gastric pressure must overcome both the native sphincter resistance and the magnetic bond between the

LINX beads. At rest, the LINX device encircles the LES with each bead resting against an adjacent bead, which avoids compression of the esophagus and allows the patient to belch or vomit as necessary. Upon swallowing, the higher pressures force the beads to expand.

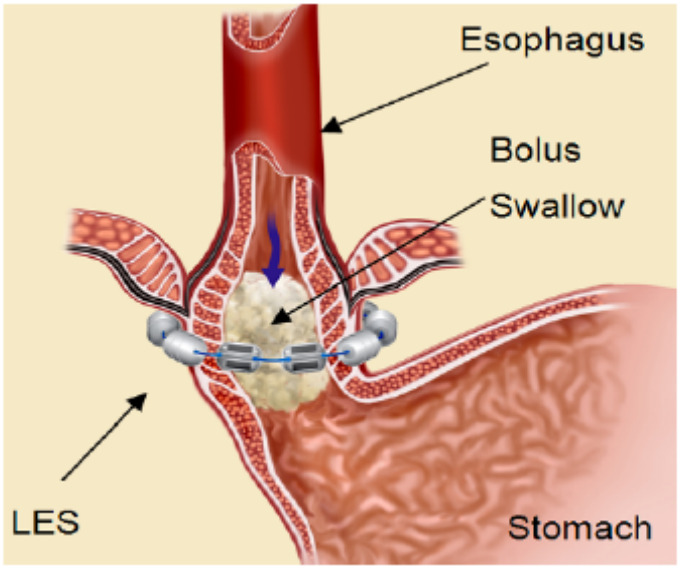
The LINX Reflux Management System can be placed laparoscopically through a port with a minimum internal diameter of 10mm or directly via laparotomy. The surgery is performed very similar to the Nissen fundoplication. Instead of mobilizing the fundus of the stomach as is done in the Nissen fundoplication procedure, the LINX device is wrapped around the outer muscle layer of the esophagus at the region of the lower esophageal sphincter (Figure 4).

Figure 4: LINX Encircling the Esophagus to Prevent Reflux



During swallowing, the pressure in the esophagus increases and the magnetic beads move apart on the titanium wire links. As the beads move apart, the magnetic forces decrease. This separation of the beads allows normal esophageal distension for food passage (Figure 5). The esophageal pressure then decreases and the magnetic beads return along the independent titanium wire links to the closed position.

Figure 5: Device Actuation During Swallowing



V. Preclinical Testing

Preclinical testing to evaluate the device prior to initiating the clinical study included performance testing of the device, biocompatibility testing, sterilization and shelf life testing, and animal testing. The results for all testing were determined to be adequate after follow-up with the sponsor.

Performance Testing
The integrity and performance of the LINX Reflux Management System was evaluated through the testing outlined in Table 1.

Table 1: Non-Clinical Performance Testing

Component	Test Description	Test Result
Complete Assembly	Mechanical Tensile Strength Test to verify tensile force required to break the device is greater than specification of 3.0 lbs.	Pass
Complete Assembly	Mechanical Tensile Strength with Suture Knots Test to verify tensile force required to break the sutured knot is greater than 3.0 lbs	Pass
Complete Assembly	Mechanical Tensile Strength with Top Knots Test to verify tensile force required to break the knot created with LSI Solutions Top Knot device is greater than 3.0 lbs	Pass
Complete Assembly	Corrosion Test Cyclic potentiodynamic polarization on device to determine device susceptibility to corrosion.	Pass
Complete Assembly without magnetic core	Surface Analysis ESCA (Electron Spectroscopy for Chemical Analysis) Test to evaluate the bead surface chemistry and determine the thickness of the native oxide	Pass
Complete Assembly	Life Cycle Testing (10 year simulated use) Test for cyclic wear on expanding and contracting device over the life of an implant. 2,190,000 saliva swallow and 1,095,000 food swallow actuations	Pass
Complete Assembly	Magnetic Field Strength Testing Magnetic field strength vs distance testing. Testing to determine if magnetic field could interfere with a pacemaker or ICD magnetic mode switch.	Pass

Biocompatibility Testing

The materials used in the LINX device are titanium, and parylene C (patient contacting), with a neodymium iron boron magnetic core (non patient contacting). Tests were selected in accordance with the FDA Guidance "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing'". The LINX device is considered to be a permanent implant and the recommended testing includes; cytotoxicity, sensitization, irritation, systemic toxicity, sub-chronic toxicity, genotoxicity, implantation, chronic toxicity, and carcinogenicity. The following tests were conducted on sterilized devices; cytotoxicity, sensitization, irritation, systemic toxicity, subchronic toxicity, and genotoxicity (Ames test). The device met the requirements for all tests. The sponsor did not conduct the standard implantation study with implants along the spine of the rabbit, because they conducted a good laboratory practices (GLP) animal studies with the device implanted for 12 months around the esophagus. Histological evaluation was conducted on the esophagus and the major organ systems. Based on this, and the fact that the materials are well characterized as implants, the sponsor did not need to conduct chronic toxicity, carcinogenicity or additional implantation testing.

The Esophageal Sizing Tool is considered a tissue contacting device of limited duration (< 24 hours). The recommended testing includes cytotoxicity, sensitization, irritation, and systemic toxicity. The patient contacting materials used in the esophageal sizing tool met the requirements of all the testing.

Sterilization and Shelf Life Testing

The proposed LINX Reflux Management System is provided sterile and is intended for single use. The LINX is packaged in a device tray and the device/tray is then placed inside a nylon reinforced pouch. The LINX device and packaging are then sterilized by gamma radiation. Sterilization validation was conduced in accordance with the guidance provided in AAMI/TIR27, "Sterilization of health care products – Radiation sterilization – Substantiation of 25 kGy as a sterilization dose –

Method VDmax," section 5.3: Procedure and ISO 11137-1, -2, and -3 "Sterilization of health care products – Radiation." Validation was conducted to demonstrate a sterility assurance level (SAL) of 10^{-6} following a minimum gamma sterilization dose of 25 kGy.

The esophageal sizing tool is supplied non-sterile. The device is to be cleaned and sterilized, by steam autoclave, by the end user. Testing was conducted and demonstrated that after cleaning and steam serialization, the sizing tool has a sterility assurance level of 10^{-6}.

After accelerated aging testing designed to simulate four years, the LINX device and the packaging were evaluated. Packaging was evaluated to ensure that the packaging did not leak or fail. The LINX device was also evaluated to determine whether the device functionality was maintained. The shelf life testing demonstrated that the packaging protects the device, maintaining performance and sterility for a four year shelf life.

Animal Testing

In addition to performance and biocompatibility testing, *in vitro* animal testing was conducted using the LINX Reflux Management System. A good laboratory practices (GLP) study was conducted to evaluate the long term (12 month) performance of the LINX device, in addition to non-GLP studies. In the GLP study, a total of 25 Sinclair Mini-Swine were implanted with the device. The animals were divided into five cohorts with sacrifice occurring at 42 days (two cohorts: n=5 w/stay stitch, n=5 w/o stay stitch), 91 days, 182 days, and 365 days post implant (Table 2).

Table 2: Animal Testing

Animal cohort	Follow-up	Purpose
1. 42 day survival n=5 animals: stay stitch n=5 animals: no stay stitch	None until sacrifice at 42 day	Acute manometry, chronic device actuation, chronic swallow function, (weight), chronic device stability, short-term histology, adverse events. Five animals were used to evaluate the need for the "stay-stitch."
2. 91 day survival n=5 animals	42 day and sacrifice at 91 day	Acute manometry, chronic device actuation, chronic swallow function, (weight), chronic device stability, intermediate-term histology, adverse events
3. 182 day survival n=5 animals	42 day, 91 day and sacrifice at 182 day	Acute manometry, chronic device actuation, chronic swallow function, (weight), chronic device stability, long-term histology, adverse events
4. 365 day survival n=5 animals	42 day, 91 day, 182 day, 273 day, and sacrifice at 365 day	Acute manometry, chronic device actuation, chronic swallow function, (weight), chronic device stability, long-term histology, adverse events

The evaluation included:

1. Acute manometry to assess the pressure of the LES region intraoperatively and to quantify any pressure changes;
2. Device actuation to determine the ability of the magnetic beads to slide apart on the independent titanium wires (actuate) during and after healing;
3. Swallow function to assess the ability to eat and maintain weight;
4. Implant stability to ensure no device migration;
5. Histological response to the implant to ensure healing was adequate and no device tissue erosion occurred; and
6. Adverse events.

During device implantation (n=25 animals) the vagus nerves were separated from the esophagus at the area of the LES and the device was wrapped around the external esophagus in this region. All animals received a stay stitch with the exception of cohort 2 (n=5 animals sacrificed at 42 days) in which no stay stitch was placed in order to evaluate the need for the stay stitch. Manometry was conducted both pre and post implant in all animals.

Study results

42 day follow-up summary. A total of 25 animals were evaluated with 10 sacrificed at day 42 (cohort 1 and cohort 2). Eight of the 25 animals had weight loss; three (3) animals with 1 kg weight loss, three (3) animals with 2 kg weight loss and two (2) animals with 4 kg weight loss. All were determined to be non-significant weight loss by the veterinary staff. One of the 4kg weight loss animals sacrificed at day 42 had an intra-operative infection at the level of the implant. Endoscopic evaluation and x-rays were unremarkable. Explant histology showed a mild to severe compression and disruption of the outer muscle layer. In two of the sacrificed animals there was severe compression and disruption of the inner muscle layer. In all animals the LINX device was covered by connective tissue and adhered muscle.

91 day follow-up summary. A total of 15 animals were evaluated with five (5) sacrificed at day 91 (cohort 3). One (1) animal had a 3 kg weight loss (determined to be non-significant). Two (2) of the animals with weight loss at day 42 had been sacrificed (study 1); the remaining four (4) evaluated at day 91 showed weight gain or had maintained the weight recorded at day 42. Endoscopic evaluation and x-rays were unremarkable. Explant histology showed that there was a moderate to severe compression of the outer muscle wall and disruption of the outer and inner muscle layers. In at least one case the inner muscle layer was moderately affected. In all animals the LINX device was covered by connective tissue and adhered muscle.

182 day follow-up summary . A total of 10 animals were evaluated with five (5)sacrificed at day 182 (cohort 4). One animal had 3 kg weight loss (determined to be non-significant), three (3) animals had weight loss of 2 kg, 4 kg and 9 kg, respectively. This weight loss was determined to be due to diet, otherwise all animals were healthy. Endoscopic evaluation and x-rays were unremarkable. Histology showed that there was mild to severe compression and disruption of the outer and inner muscle layers. In some areas there was no muscle between the device beads. In some cases there was little or no muscle from the outer layer remaining along the inner border of the beads. However, the beads were completely surrounded by muscle.

273 day follow-up summary. five animals were evaluated with none sacrificed (cohort 5). There was no additional weight loss and animals that lost weight had all gained weight. Endoscopic evaluation and x-rays were unremarkable.

365 day follow-up summary. A total of five (5) animals were evaluated and sacrificed at day 365 (cohort 5). Generally (4/5 animals) the outer muscular layer was multifocally displaced by the beads. The inner muscle layer was seen on some sections to be moderately compressed. There was a dense fibrous encapsulation of the beads seen in several sections. The histologic changes noted at 12 months post implantation were not significantly different than that noted at 6 months post implantation. Endoscopic evaluation and x-rays were unremarkable.

Overall findings

At necropsy all animal organs appeared normal. Five animals (cohort 2) had no stay stitch anchoring the device to the muscular portion of the esophagus. It was determined that this stitch was not required. All 25 animals studied showed no signs of device migration.

At sacrifice, all animals had devices encapsulated in fibrous tissue which appeared histologically stable. Healing appeared stable and complete by three (3) months. One animal had histologic findings consistent with an intra-operative infection. No other adverse event was noted with this animal.

The GLP study results demonstrate device safety and satisfactory device actuation at each time point out to day 365. Gross necropsy showed no adverse effects with minimal to moderate adhesions. Histologic results demonstrate the LINX device adequately healed within the esophageal tissue.

VI. Clinical Studies

Introduction

The purpose of the feasibility and pivotal trials was to evaluate the safety and effectiveness of the LINX device in the treatment of Gastroesophageal Reflux Disease (GERD). The device is indicated for those subjects diagnosed with pathologic GERD as defined by abnormal pH testing and who continue to have chronic GERD symptoms despite anti-reflux drug therapy. The device is intended to augment the competence of the Lower Esophageal Sphincter (LES) to reduce or eliminate gastric reflux.

A. FEASIBILITY STUDY

A feasibility study was performed to collect safety information, performance data, and develop procedural optimization for the LINX device in the treatment of GERD. The feasibility study was approved on September 29, 2006, for four investigational sites and 10 subjects. On October 5, 2007, the number of subjects approved for the feasibility study was increased to 40 enrolled with up to 16 subjects to be implanted. In addition to information on subjects enrolled in the IDE, the sponsor provided information on subjects enrolled in Europe in the annual progress reports for this study. The data summarized below include both data from the European sites and data from the US feasibility study.

1. Design:

This was a prospective, non-randomized trial in which each subject served as his or her own control.

2. Patient Demographics:

A total of 44 subjects (11 US and 33 European), reported to have confirmed GERD and incomplete response to proton pump inhibitor therapy, were implanted with the device at 4 investigational sites (2 US and 2 European). At baseline (Table 3), 59% percent of the subjects were male and the mean age was 42.8. The mean GERD-HRQL score was 26.6.

Table 3: Baseline Demographics

Characteristic	Mean (Range)
Age (years)	42.8 (19-71)
Gender	M 59.1% F 40.9%
BMI	25.7 (19-38)
% time pH <4	11.9% (2.7-38.2)
GERD-HRQL	26.6 (10-39)

3. Endpoints:

There were no statistical hypotheses for this study; however, the objectives were the following:

- Safety: to evaluate the incidence of all adverse events up to 60 months post implant.
- Effectiveness: to monitor the improvement of GERD symptoms and LES function at various time points up to 60 months post implant and optimize the implant technique.

Effectiveness was characterized by:

1. Reduction of GERD symptoms as assessed by:
    - Subjective measurements using the GERD-HRQL
    - Evaluation of PPI use

2. LES function characterized by:
    - 24 hour pH profile
    - Manometry/motility
    - Barium esophagram.

GERD-HRQL

In using the GERD-HRQL (Health Related Quality of Life) Scale Questionnaire, subjects were asked to rate their GERD symptoms on a scale from 0 to 5 for the following 10 questions.

1. How bad is your heartburn?
2. Heartburn when lying down?
3. Heartburn when standing up?
4. Heartburn after meals?
5. Does heartburn change your diet?
6. Does heartburn wake you from sleep?
7. Do you have difficulty swallowing?
8. Do you have bloating or gassy feelings?
9. Do you have pain with swallowing?
10. If you take medication, does this affect your daily life?

The questionnaire also asked subjects to answer the question "How satisfied are you with your present condition", with potential answers of "Satisfied", "Neutral", or "Dissatisfied".

As noted above, each item on the GERD-HRQL questionnaire was rated on a scale of 0 to 5. These ratings are defined below:

0 = No symptoms
1 = Symptoms noticeable but not bothersome
2 = Symptoms noticeable and bothersome but not every day
3 = Symptoms bothersome every day
4 = Symptoms affect daily activities
5 = Symptoms are incapacitating – unable to do activities

Total scores on the GERD-HRQL could range from a minimum of 0 to a maximum of 50, with larger values indicating more severe GERD.

The GERD-HRQL questionnaire was to be completed both on and off PPI therapy. For the "off PPI" GERD-HRQL questionnaire, subjects were instructed to discontinue any GERD medications for at least seven (7) days prior to completing the questionnaire with the exception of antacids, which may be taken up until the morning of the visit.

4. Summary of Feasibility Clinical Data Results:

a. Safety:

Endoscopy was performed to evaluate for device erosion (Table 4); no device erosions occurred during the study.

Table 4: Device Erosion

Visit	N	Device erosion
3 months	39	No
12 months	35	No
24 months	26	No
36 months	25	No

Abdominal/Chest X-ray was performed to evaluate if the device has migrated from the implant location (Table 5); there have been no reports of device migration.

Table 5: Device Migration

Visit	N	Device migration
3 months	19	No
12 months	26	No
24 months	26	No
36 months	25	No

Barium esophagram was performed to evaluate for swallow function in 35 patients at 3 months and 36 patients at 12 months. No adverse events were reported as a result of the test findings.

Manometry and motility testing was performed to characterize esophageal swallow and sphincter functions, including LES length, LES resting tone, and peristaltic functions. Testing was performed on 24 subjects at three months and 26 subjects at 12 months post implantation. One subject underwent testing 27 days post implant and showed 50% aperistalsis. At 3 months, manometry/motility testing showed 80% normal peristalsis, which then decreased again to 58% normal peristalsis at 12 months. This subject reported ongoing intermittent dysphagia; however, answers to the swallow associated questions on the GERD-HRQL follow-up at 12 months indicated no symptoms of difficulty swallowing or pain with swallowing.

Adverse Events:
A total of 24 of 44 subjects (54.5%) implanted with the device experienced adverse events related to the device and/or procedure. The most common adverse event experienced by subjects was dysphagia (22 events in 20 subjects). Although most cases resolved within approximately three months, two subjects required dilation in the area of the gastroesophageal junction (GEJ), and one (1) subject had the device removed.

There were four anticipated serious adverse events; three of which resulted in explant.

- One (1) subject experienced dysphagia initially following the procedure and presented with ongoing dysphagia at 6 month follow-up. At 226 days post-procedure, the subject was hospitalized and the device was removed laparoscopically, without complication. The investigator reported that the subject's dysphagia was improving at approximately one month post-explant. This subject subsequently had a fundoplication procedure.

- One subject continued to experience recurrent heartburn, the device was removed (day 1302) and the subject underwent a Nissen fundoplication.

- One (1) subject experienced neurological and vascular symptoms unrelated to the device and procedure. The symptoms resulted in a consult with a neurologist who recommended an MRI. The study subject requested removal of the device in order to undergo this MRI procedure.

- One (1) subject experienced chest pain resulting in hospitalization 22 days following implant. This event was resolved within 55 days of implant.

During the implantation of the device, the following events were observed.

- In one subject, the anterior vagus nerve bundle was included inside the device during implantation
- Three devices were attempted to be implanted, but the surgeon did not properly tighten the sutures prior to securing them-in each case; a 2nd device was used to complete the procedure.
- One device was implanted, subsequently determined to be an incorrect size (too large), and then removed and exchanged for a 2nd device at the time of implant.
- One device was opened and readied for implant, but a repeat sizing procedure resulted in a different size device being used.

- One device could not be secured because the sutures became tangled during the procedure.

b. Effectiveness:

The primary performance objectives were (1) to evaluate improvements in the subject's GERD symptoms by assessing GERD-HRQL scores, and (2) to evaluate reduction in PPI use.

Table 6 shows measures of improvement in GERD symptoms as assessed by GERD-HRQL and self-reported satisfaction by visit. By three months, GERD-HRQL scores improved by at least 50% in 97% of subjects. This improvement was maintained through 36 months.

Table 6: Improvement in GERD Symptoms by Visit

Visit	N	% Subjects with improvement in GERD-HRQL score by ≥ 50%	% Subjects reporting "satisfied" with current condition
3 months	37	97.3%	83.8%
12 months	39	97.4%	87.2%
24 months	35	88.6%	80%
36 months	27	96.3%	92.6%

Table 7 shows improvement in PPI use by visit. By three months, 88.2% of subjects had eliminated or reduced their PPI use by at least 50%. This improvement was maintained out to 36 months.

Table 7: Improvement in PPI Use by Visit

Visit	N	% Subjects off PPI or reduced therapy By ≥ 50%
3 months	34	88.2%
12 months	39	89.7%
24 months	35	82.9%
36 months	32	87.5%

Table 8 summarizes the percentage of subjects with acid exposure normalized or reduced by at least 50% by visit:

Table 8: Percent of Subjects with at least 50% Reduction in Acid Exposure

Visit	N	% Subjects with normal pH or ≥ 50% reduction in acid exposure
3 months	38	78.9%
12 months	39	79.5%
24 months	20	90%
36 months	1	100%

The data demonstrates that improvement in GERD symptoms, as well as PPI use, was achieved in a majority of subjects, with few serious adverse events.

B. PIVOTAL STUDY

1. Design:

This was a prospective, multi-center, single-arm study with subjects serving as their own control.

2. Study Endpoints:

a. Primary Safety Endpoint

The primary safety endpoint was the rate of occurrence of serious device- and procedure-related adverse events at 12 months post implantation. This was assessed by endoscopy, abdominal/chest X-rays, manometry, and barium esophagrams.

The following definitions were used for rating the severity of adverse events:

- Mild: Awareness of signs of symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms may not require medication or a medical evaluation; signs of symptoms are transient.
- Moderate: Discomfort intense enough to cause interference with usual activities.
- Severe: Incapacitating with inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical evaluation and or treatment.

b. Primary Effectiveness Endpoint:

The primary effectiveness endpoint was reduction in total distal esophageal acid exposure time assessed by esophageal pH testing.

Esophageal pH testing was performed with the Bravo pH Monitoring System in all subjects at both baseline and 12 months. This test directly measures acid in the esophagus over a period of time; typically 24 to 48 hours by using a capsule clipped endoscopically in the distal esophagus 6 cm above the squamocolumnar junction. If the pH evaluation is for longer than 48 hours, the total distal acid exposure time will be recorded as a 24 hour average (e.g., 48 hour Bravo testing) The pH sensor measures acid events, defined by pH<4 including:

- Total time pH <4 (%)
- Upright time pH <4 (%)
- Supine time pH <4 (%)
- Total number of reflux episodes
- Number of reflux episodes >5 min
- Longest reflux episode (min)
- Total DeMeester Score (composite of above parameters)

Success was defined as normalized pH (pH <4 for ≤4.5% of total monitoring time) or alternatively, at least a 50% reduction in total distal acid exposure, even if the pH was not normalized.

The predetermined success criteria was at least 60% of subjects implanted with the device would have at least a 50% improvement in 24 hour pH, as indicated by the lower bound of a 97.5% confidence interval for the success rate.

c. Secondary Effectiveness Endpoints:

1. Reduction in GERD symptoms defined by a validated GERD-HRQL questionnaire.
    - Subject-level success was defined as a reduction of ≥ 50% in the total GERD-HRQL score at 12 months post implantation as compared to baseline score off PPI therapy.
    - This endpoint would be met if the lower bound of a 97.5% confidence interval for the success rate was at least 60%.
2. Reduction in PPI use
    - Subject-level success was defined as a reduction in PPI daily use by ≥ 50% at 12 months post implantation as compared to a subject's baseline PPI use.
    - This endpoint would be met if the lower bound of a 97.5% confidence interval for the success rate was at least 60%.

d. Additional Data

During the study there were other assessments that were evaluated that were not considered secondary endpoints.

- Foregut Symptoms Questionnaire – subjects were asked to rate their possible GERD related symptoms numerically on various scales for each symptom (Table 9) .

Table 9: Symptoms Assessed on Foregut Questionnaire

Symptom	**Assessments**
Heartburn	Severity • None • Minimal – occasional episodes • Moderate – primary reason for visit • Severe – interfering with activities of daily life Frequency Food correlation
Chest Pain	Severity • None • Minimal – occasional episodes • Moderate – primary reason for visit • Severe – interfering with activities of daily life Frequency
Regurgitation	Severity • None • Minimal – occasional episodes • Moderate – primary reason for visit • Severe – interfering with activities of daily life Frequency Quality (acid, bitter, food)
Lung problems (extra-esophageal)	Extra-esophageal symptoms seen with GERD: Recurrent cough, nocturnal cough, recurrent pneumonitis, asthma, change of voice
Difficulty swallowing	Severity • None

	• Minimal – occasional episodes • Moderate – primary reason for visit • Severe – interfering with activities of daily life Frequency
Pain with swallowing	No/Yes Pain with Swallowing and Frequency
Pain	Location (above stomach, upper abdomen, lower abdomen) Frequency Associations with means, nighttime (lying down) Intensity (mild, moderate, severe)
Nausea/vomiting	Severity • None • occasional episodes of nausea • frequent and prolonged nausea, no vomiting • continuous nausea, frequent vomiting Frequency Ability to vomit: Yes/No/No need to vomit
Belching	Frequency: None, Occasionally, Frequently or Continuously Ability to belch: Yes/No
Bloating	Frequency: None, Occasionally, Frequently or Continuously
Increased Gas/Rectum	Frequency: None, Occasionally, Frequently or Continuously
Bowel Movements	Normal, Constipation, Diarrhea, Alteration of constipation and diarrhea Frequency

This questionnaire was to be completed while the subject was off PPI therapy (subjects were instructed to discontinue any GERD medications for at least 7 days prior to completing, with the exception of antacids, which may be taken up until the morning of the visit).

- Esophagitis – assessed using the LA classification scheme (Table 10).

Table 10: LA Classification for Esophagitis

Grade	Definition
A	One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length.
B	One or more mucosal breaks more than 5mm in maximum length, but not continuous between the tops of two mucosal folds.
C	Mucosal breaks that are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference.
D	Mucosal breaks, which involve at least 75% of the esophageal circumference. The presence or absence of strictures, ulcers, and/or Barrett's esophagus must be noted separately, e.g., "Grade B with stricture."

Note: A lesion was not considered to be present if there were no breaks (erosions) in the esophageal mucosa (edema, erythema, or friability).

- Information was also collected on procedural success rate, time of overall procedure, and length of hospital stay

- DeMeester Score - The DeMeester Score is a global measure of esophageal acid exposure. It includes the primary endpoint in combination with five other components:
    - % upright time pH < 4
    - % supine time pH < 4
    - Total number of reflux episodes
    - Number of reflux episodes > 5 minutes
        - Longest reflux episode (minutes)

These other components were examined as well.

3. Patient Selection Criteria:

Inclusion Criteria:

1. Subjects must be at least 18 years of age and at least the minimum Age of Majority according to applicable State or Country Law and must be less than 75 years of age with a life expectancy of > 3 years.
2. Subject is a suitable surgical candidate, i.e., is able to undergo general anesthesia and laparoscopic surgery.
3. Documented typical symptoms of gastroesophageal reflux disease for longer than 6 months (regurgitation or heartburn which is defined as a burning epigastric or substernal pain which responds to acid neutralization or suppression).
4. Patient requires daily proton pump inhibitor or other anti-reflux drug therapy.
5. Total Distal Ambulatory Esophageal pH must meet the following criteria: pH < 4 for ≥ 4.5% of the time Note: Subjects shall have discontinued any GERD medications at least 7 days prior to testing.
6. Subjects with symptomatic improvement on PPI therapy demonstrated by a GERD-HRQL score of ≤ 10 on PPI and ≥ 15 off PPI, or subjects with a ≥ 6 point improvement when comparing their on PPI and off PPI GERD-HRQL score.
7. GERD symptoms, in the absence of PPI therapy (minimum 7 days).
8. If the subject is of child bearing potential she must have a negative pregnancy test within one week prior to implant and must agree to use effective means of birth control during the course of the study.
9. Subject is willing and able to cooperate with follow-up examinations.
10. Subject has been informed of the study procedures and the treatment and has signed an informed consent form.

Exclusion Criteria:

1. The procedure is an emergency procedure
2. Currently being treated with another investigational drug or investigational device
3. History of gastroesophageal surgery, anti-reflux procedures, or gastroesophageal/ gastric cancer
4. Any previous endoscopic anti-reflux intervention for GERD and/or previous endoscopic intervention for treatment of Barrett's esophagus
5. Suspected or confirmed esophageal or gastric cancer
6. Any size hiatal hernia > 3 cm as determined by endoscopy

7. Distal esophageal motility (average of sensors 3 and 4) is less than 35 mmHg peristaltic amplitude on wet swallows or < 70% (propulsive) peristaltic sequences
8. Esophagitis – Grade C or D (LA Classification)
9. BMI > 35
10. Symptoms of dysphagia more than once per week within the last 3 months
11. Diagnosed with Scleroderma
12. Diagnosed with an esophageal motility disorder, such as, but not limited to, Achalasia, Nutcracker Esophagus, or Diffuse Esophageal Spasm or Hypertensive LES
13. Subject has a history of or known esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc.)
14. Subject has esophageal or gastric varices
15. Subject has Barrett's esophagus
16. Cannot understand trial requirements or is unable to comply with followup schedule
17. Pregnant or nursing, or plans to become pregnant during the course of the study
18. Medical illness (i.e., congestive heart failure) that may cause the subject to be non-compliant with or unable to meet the protocol requirements or is associated with limited life expectancy (i.e., less than 3 years)
19. Diagnosed psychiatric disorder (e.g., bipolar, schizophrenia, etc.); subjects that exhibit depression that are on appropriate medication(s) are allowable
20. Suspected or known allergies to titanium, stainless steel, nickel or ferrous materials
21. Subject has an electrical implant or metallic, abdominal implants

4. Subject Follow Up Evaluation:

The follow-up testing conducted for this study is shown in Table 11. Although 24 hour esophageal pH testing is the basis of the primary effectiveness endpoint (measured at 12 months), this test was not conducted at any follow-up visit after 12 months. Subjects enrolled in this study were to be followed for a total of five years.

Table 11: Schedule of Follow-up Visits and Procedures

Screening	Implant	48 hour/Discharge	1 Week	3 months	6 months (Office Visit)	12 months (Office Visit)	24 months (Office Visit)	36 months	48 months	60 months (Office Visit)	Type of Follow-up
X						**X**					Health History
X				**X**	**X**	**X**	**X**	**X**	**X**	**X**	GERD-HRQL Questionnaire
X				**X**	**X**	**X**	**X**	**X**	**X**	**X**	Foregut Symptom Questionnaire
X				**X**	**X**	**X**	**X**	**X**	**X**	**X**	PPI, H2, Antacid and other Medication Use

X						**X**					Esophageal pH
X						**X**					Manometry/Motility
X	**O**					**X**	**X**			**X**	EGD Endoscopy
X						**X**					Barium Esophagram (Fluoroscopy)
	X					**X**	**X**			**X**	Abdominal/Chest X-ray
	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	Adverse Events

Assessment for the primary effectiveness endpoint was performed at 12 months and assessments for secondary effectiveness endpoints were performed at 12 and 24 months (±60 days) from implant date. Adverse events were reported to be recorded throughout the study.

5. Statistical Plan:

Minimum sample size requirements were calculated based on the primary effectiveness objective using StatXact 5.0 software under an exact, one-sided test for one binomial population.
The following hypothesis was tested:

$$\mathbf{H_o: \Pi \leq 0.60}$$
$$\mathbf{H_a: \Pi > 0.60,}$$

where Π is the proportion of subjects meeting the success criterion of either pH normalization or at least 50% reduction in total distal acid exposure.

Sample size was calculated under the following assumptions:

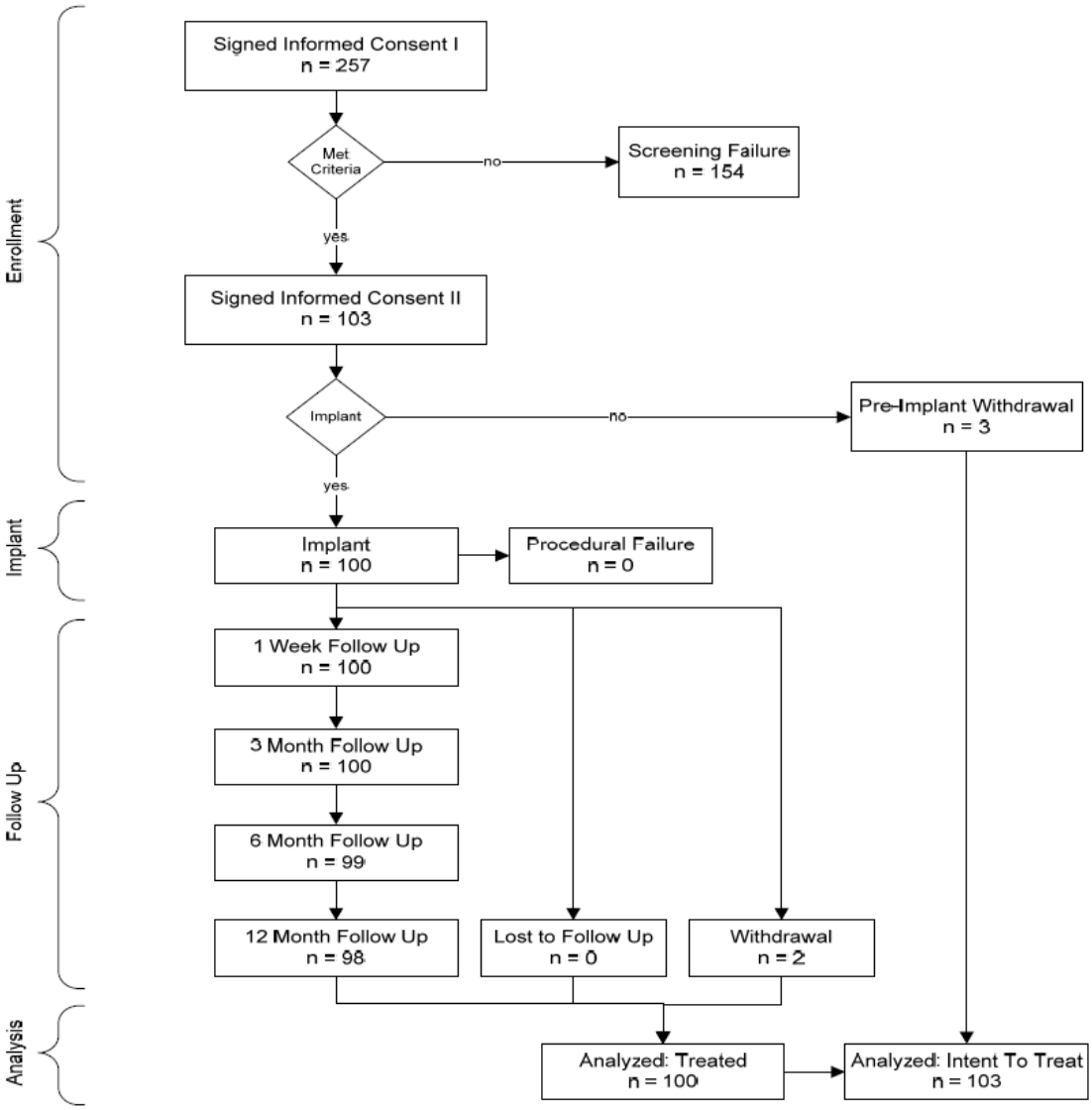
- Significance level (alpha) = 2.5%
- Power = 80%
- Expected underlying success rate for the treatment group = 75%
- Under the assumptions outlined above, a minimum of 80 evaluable subjects were required to test the stated performance hypothesis. To allow for up to 20% attrition (e.g. losses to follow-up, death, withdrawal), up to 100 subjects were implanted. To allow for screening failures, change of consent, etc. the enrollment limit will be 300 subjects. With 80 evaluable subjects, the primary safety endpoint will be estimated with a precision of approximately 6.6% assuming an underlying serious, device and procedure related adverse event rate of 10%. This level of precision was thought to be sufficient to adequately assess the safety of the device and procedure.

Study Results

6. Patient Accountability:

There were 257 subjects that agreed to take part in the study, 154 of these subjects failed screening and were not eligible to participate. The Informed Consent was signed by 103 subjects. Of these subjects, a total of 100 were implanted with the LINX System. The three subjects not implanted with the LINX device were withdrawn due to the limit of 100 implants being reached (n=2) and allergy to nickel (n=1). The Intent-to-Treat Group and Treated Group consisted of 103 and 100 subjects, respectively. The analyses of the effectiveness endpoints were based on the Treated Group see (Figure 6) below.

Figure 6: Subject Disposition



The primary endpoint was to be measured at 12 months post device implantation.
There were a total of five explants prior to 24 months. At the 24-month follow up, 95 subjects still had the device implant. Two subjects withdrew from the study and three subjects did not return for the follow-up visit, for a total of 90 subjects that were evaluated at 24 months (Table 12).

Table 12: Subject Disposition through 24 months

Visit	Total Number Implanted	Number Explanted Prior to 24M	Number Expected at 24M	Number Withdrawn / LTF at 24M	Number Non-Completions	Number Visits at 24M	Compliance % (n/N)
24 Months	100	5	95	2	3	90	94.7% (90/95)

7. Patient Demographics:

A total of 100 subjects (96 US and 4 European) were implanted with the device, at 14 investigational sites (13 US and 1 European).

Demographics and baseline values are summarized briefly in Table 13.

Table 13: Baseline Demographics

Characteristic	Mean (Range)
Age (years)	50.4 (18.3-74.7)
Gender	M 52% F 48%
Race	Caucasian 96% Hispanic 3% Other 1%
BMI	27.9 (19.8-34.7)
% time pH <4	11.6% (4.8%-25.4%)
GERD-HRQL	26.6 (11-47)

The following items further characterize the study subjects at baseline:

- Mean duration of GERD was 12.8 years
- Mean duration of PPI use was 6.3 years
- All subjects were reported to be on daily PPI therapy
- Mean GERD-HRQL score off PPI therapy was 26.6 and on PPI therapy was 12.0
- Total % pH Time <4 was 11.6
- 32 subjects had a hypotensive LES resting tone < 10 mmHg
- 40% of subjects had Grade A or B esophagitis
- 56% of subjects had a hiatal hernia
- Subjects were reported to have an average of 78.6 episodes of heartburn /week
- Subjects were reported to have an average of 27.9 episodes of regurgitation/week

8. Implantation Procedure:

All subjects were implanted with the device by laparoscopy and completed the procedure with no cross-over to an open surgical technique or Nissen fundoplication. Academic sites performed 51 implants and community sites performed 49 implants. Half the subjects (50/100) were discharged the same day as surgery, and the other half (50/100) were discharged the next day.

Procedure times, defined as the time from which all laparoscopic ports were in place to when the first port was removed, ranged from 7 minutes to 125 minutes.

The LINX device is available in sizes ranging from 10 to 18 beads; most subjects (46%) were implanted with a 14 bead LINX device (Table 14)

Table 14: Device Size Implanted

Device Size Implanted	% (n/N)
12-Bead	5.0% (5/100)
13-Bead	22.0% (22/100)
14-Bead	46.0% (46/100)
15-Bead	25.0% (25/100)
16-Bead	2.0% (2/100)

9. Summary of Clinical Data Results:

a. Safety:

Endoscopy was performed to evaluate for device erosion. Ninety-seven (97) subjects were evaluated at 12 months and no device erosions were seen. One subject did have atypical erythema that was considered separate and different from the Grade A esophagitis also found at 12 months.

Abdominal/Chest X-ray was performed to evaluate for device migration. Ninety-five subjects were evaluated at 12 months and no device migration was seen.

Barium esophagram was performed on 96 subjects at 12 months to evaluate for swallow function. Three of these subjects had abnormal swallow function. These findings were deemed to not be highly clinically significant since there was no associated dysphagia, however, one of these subjects did have to have an esophageal dilation.

Manometry and motility testing was performed to characterize esophageal swallow and sphincter functions. Ninety three (93) subjects completed manometry as 12 months. Three out the 32 subjects who had a hypotensive LES resting tone < 10 mmHg at baseline, remained hypotensive (9.7%; 3/31). Fifteen (15) subjects had <70% effective swallows, and four subjects had distal esophageal amplitude <35 mmHg. One subject [redacted] had ongoing complaints of dysphagia and abnormal motility (defined as <70% effective swallows and/or distal amplitude <35 mmHg) at 12 months.

Adverse Events:

Seventy-six (76) of the 100 subjects (76.0%) implanted with the LINX device experienced a total of 162 adverse events related to the device and/or procedure (Table 15)

Table 15: Adverse Events Related to or Relationship to Device or Procedure Unknown

	Related or Unknown		Mild		Moderate		Severe	
Adverse Event	**AEs (n)**	**Subj. % (n)**	**AEs (n)**	**Subj. % (n)**	**AEs (n)**	**Subj. % (n)**	**AEs (n)**	**Subj. % (n)**
Total	162	76% (76)	108	65% (65)	42	28% (28)	12	10% (10)
Dysphagia	76	68% (68)	54	49% (49)	17	16% (16)	5	5% (5)
Pain	25	24% (24)	8	8% (8)	13	13% (13)	4	4% (4)
Stomach Bloating	15	14% (14)	13	12% (12)	2	2% (2)	0	0%
Nausea	8	7% (7)	4	3% (3)	2	2% (2)	2	2% (2)
Odynophagia	8	8% (8)	4	4% (4)	3	3% (3)	1	1% (1)
Other: HICCUPS	8	8% (8)	7	7% (7)	1	1% (1)	0	0%
Inability to belch or vomit	6	6% (6)	5	5% (5)	1	1% (1)	0	0%
Other: DECREASED APPETITE	4	4% (4)	4	4% (4)	0	0%	0	0%
Other: BELCHING	2	2% (2)	2	2% (2)	0	0%	0	0%
Other: FLATULENCE	2	2% (2)	2	2% (2)	0	0%	0	0%
Other: WEIGHT LOSS	2	2% (2)	2	2% (2)	0	0%	0	0%
Other: FOOD IMPACTION	1	1% (1)	0	0%	1	1% (1)	0	0%
Other: GLOBUS SENSATION	1	1% (1)	1	1% (1)	0	0%	0	0%
Other: IBS/DYSPEPSIA	1	1% (1)	1	1% (1)	0	0%	0	0%
Other: REGURGITATION OF STICKY MUCUS	1	1% (1)	0	0%	1	1% (1)	0	0%
Other: UNCOMFORTABLE FEELING IN CHEST	1	1% (1)	1	1% (1)	0	0%	0	0%
Vomiting	1	1% (1)	0	0%	1	1% (1)	0	0%

The most common adverse event experienced by subjects was dysphagia (76 events in 68 subjects). Eighteen (18) subjects at seven (7) sites underwent esophageal dilation for dysphagia, odynophagia, regurgitation or burning sensation in throat.

- 12 of these patients had ≥ 2 dilations
- 10 of these patients continued to have symptoms.

The 2nd most common event experienced by subjects was pain (25 events in 24 subjects).

There were nine serious adverse events reported in six subjects (Table 16) related to the device or procedure,

Table 16: Serious Adverse Events Related to Device and/or Procedure

Serious Adverse Event	Events (n)	Subjects % (n)
Total	9	6% (6)
Dysphagia	3	3% (3)
Nausea	2	2% (2)
Vomiting	2	2% (2)
Odynophagia	1	1% (1)
Pain[1]	1	1% (1)

[1]Adjudciated with a relationship of Unknown to device and/or procedure

Regarding the time to onset of the adverse events (Table 17), there were 149 device or procedure related adverse events that occurred between 0 and 180 days. After 180 days, there were 13 device or procedure related adverse events with one event being related to the device or procedure. This subject experienced chest pain, nausea, and symptoms of indigestion (day 235 post implant).

Table 17: Days to Onset of Adverse Event

Adverse Event Type	0 – 90 Days	90-180 Days	>180 Days
All Adverse Events	70.3% (218/310)	10.3% (32/310)	19.4% (60/310)
Related to device/procedure or unknown relationship	84.0% (136/162)	8.0% (13/162)	8.0% (13/162)
Serious	41.2% (7/17)	35.3% (6/17)	23.5% (4/17)
Serious related to device/procedure or unknown relationship	77.8% (7/9)	11.1% (1/9)	11.1% (1/9)

Explants:

There were five (5) subjects who had the device explanted. Three subjects had the device explanted for dysphagia, with two (2) of these subjects then electing to have a Nissen fundoplication.

- One (1) subject with history of severe heartburn, severe regurgitation, frequent and prolonged nausea, experienced nausea coupled with dysphagia within two weeks of device implantation. The subject was hospitalized for management of these symptoms, including balloon dilation in the region of the GEJ. The symptoms improved as a result of the dilation; however, dysphagia and nausea persisted. Thirty days post-implant, the

subject requested to have the device removed and subsequently underwent a fundoplication procedure.

- One subject with history of GERD manifesting with heartburn and regurgitation started with dysphagia 5 days after device implantation. Esophageal dilation performed 18 days post implant did not resolve the symptoms and the subject underwent manometry/motility testing where it was determined that the subject had a loss of esophageal motility. The Investigator described the event as achalasia secondary to the anti-reflux procedure, requiring device removal for symptom relief. The device was removed from this subject on post-operative day 21 without complication, and it was reported that symptoms have resolved.

- One subject reported dysphagia 5 days post-implant and odynophagia 7 days post-implant. Esophageal dilations of the GEJ were performed on post-implant days 29 and 49. The subject continued to have dysphagia and the device was removed 93 days post implant without complication. The dysphagia resolved and the subject was withdrawn from the study.

- One subject had recurrent GERD symptoms and elected to have the device removed so a Nissen fundoplication could be performed. The device removal was performed 1302 days post-implant.

- One subject had intermittent vomiting beginning about 3 months after device implantation. During the follow-up period, the subject underwent testing to identify the cause of vomiting. In June 2010, a diagnosis of H. Pylori was made and medication started. However, the intermittent vomiting continued and the device was explanted on June 28, 2010. No conclusive cause was identified for vomiting and the Investigator reported the cause of the AE as unknown. At last follow-up in July 2010, the subject reported continued vomiting on a weekly basis. The Investigator reported the cause as unknown.

<u>There were two serious adverse events that did not result in explant of the device.</u>

- One subject reported nausea and vomiting 2 days post-implant. The subject was hospitalized and symptoms were reported to have subsequently resolved.

- One subject had a 3 cm hiatal hernia at baseline that was repaired at the time of device implantation on June 3, 2009. The subject initially reported improvement in GERD symptoms and cessation of PPI use. Subsequently, the subject reported return of mild heartburn and regurgitation. During the l2-month follow-up, a 2 cm hiatal hernia was noted by the Investigator during the upper endoscopy and was subsequently repaired.

Unanticipated adverse events, described as “not serious” are shown in Table 18. The sponsor notes that although these events are considered “unanticipated” they are not unexpected after anti-reflux surgery. The most common event was “hiccups” which occurred in eight subjects.

Table 18: Unanticipated Adverse Event, Not Serious

Unanticipated Adverse Event	Events (n)	Subjects % (n)
Total	11	11% (11)
Other: HICCUPS	8	8% (8)
Other: BELCHING	1	1% (1)
Other: FOOD IMPACTION	1	1% (1)
Pain[1]	1	1% (1)

[1] Oringally reported by site and ajduciated as esophageal spasm before CEC decided to reclassify all esophageal spasm as pain and related.

Adverse events, reported as having unknown causality to the device or the procedure, are shown in Table 19. There were four reports of "pain" and three reports of "decreased appetite."

Table 19: Adverse Events with Unknown Relationship to Device or Procedure

Unknown Relationship to Device/Procedure Adverse Event	Events (n)	Subjects % (n)
Total	11	11% (11)
Pain	4	4% (4)
Other: DECREASED APPETITE	3	3% (3)
Nausea	1	1% (1)
Other: FLATULENCE	1	1% (1)
Other: IBS/DYSPEPSIA	1	1% (1)
Other: REGURGITATION OF STICKY MUCUS	1	1% (1)

FDA Comments on Safety

- Although this device is intended for patients who would not otherwise opt for Nissen fundoplication, some of the subjects in the study who had the device explanted did subsequently undergo a fundoplication.

- Dysphagia was the most common adverse event seen in this study (as well as the feasibility study). In this study, seven (7) subjects experienced symptoms of odynophagia/dysphagia that started after 180 days (182-605). In addition, several

subjects had odynophagia and/or dysphagia that took over 180 days to resolve (maximum time noted 447 days).

- A 270^{o} fundoplication is recommended in patients with abnormal esophageal peristalsis due to its theoretical advantage of limiting dysphagia[3]. Though the number of subjects is small, dysphagia was seen to resolve in the majority of subjects who had the device explanted. Although it appears that device implantation and use did not cause any long term adverse effects upon removal, it raises the question of should the potential risk of dysphagia requiring intervention such as dilation, or ultimately, device removal, outweigh the clinical benefit of device implantation and use the way it is currently designed.

b. Effectiveness:

A subject met the primary endpoint at 12 months if either of the following criteria were met:

- there was normalization of pH, with normalization defined as pH < 4 for $\leq$ 4.5% of monitoring time, or
- there was a reduction of at least 50% in total time that pH <4, relative to baseline.

Testing was to be done off PPIs. The specified analysis cohort for the primary effectiveness analysis was the treated population, which included all implanted subjects. The sponsor did not perform esophageal pH testing beyond the 12-month follow-up, thus this endpoint could not be evaluated at 24 months.

In addition to the primary endpoint, the DeMeester Score were also examined. Table 20 summarizes the individual components of the pH testing for the DeMeester Score at baseline and 12 months.

Table 20: pH Parameters of Esophageal Acid Exposure

DeMeester Components	Normal Values[1]	Baseline N=100	12 Months N=96[2]
Total time pH<4 (%)	5.3	11.6±4.7 (10.9) N=100	5.1±4.8 (3.3) N=96
Upright time pH<4 (%)	6.9	14.0±7.2 (12.7) N=100	6.5±5.8 (4.3) N=96
Supine Time pH<4 (%)	6.7	7.8±7.2 (6.0) N=98	2.9±5.8 (0.4) N=95
Number of Episodes pH<4	36.8	175.0±81.7 (161.0) N=100	82.8±67.6 (67.0) N=96
Number of Episodes > 5 minutes	1.2	12.4±6.7 (12.0) N=99	6.1±6.8 (4.0) N=96
Longest Episode (min)	N/A	37.4±24.4 (29.0) N=99	19.7±20.9 (13.0) N=96
DeMeester Score	N/A	41.0±16.3 (36.6) N=97	18.7±17.3 (13.5) N=95

[1]. Normal values based on Bravo pH test as reported by Pandolifino et al.
[2]. Two subjects were withdrawn prior to 12 months, and two others did not complete pH testing

Although the primary endpoint was agreed upon, it is the composite DeMeester Score that has been shown to be the most reliable measurement of a therapeutic acid suppression regimen or an effective antireflux operation, having the highest sensitivity and specificity for GERD, both 96%. As such it is important to note that of the total number of patients that had pH testing at 12 months, only 52% had a normal DeMeester Score (defined as < 14.7[2]).

The following table (Table 21) summarizes the analysis for the primary effectiveness endpoint (pH testing) . The observed success rate was 64% (64/100). Note that the lower limit of the confidence interval is 53.8%, which falls below the pre-specified success threshold of 60%; thus the results for this endpoint do not support the claim that the success probability is greater than 60%.

Table 21: Primary Effectiveness Endpoint: Bravo pH Normalization or ≥ 50% Reduction at 12 months

Primary Efficacy Endpoint	% Successful (Number of Subjects/Total)	Lower 97.5% Exact Binomial Confidence Limit	p-value[1]
Bravo pH • Normalization (≤4.5%) OR • ≥ 50% reduction from baseline	64.0% (64/100)	53.8%	0.24

[1]From one-sided, binomial exact test against the null hypothesis of ≤ 60%.

There were 64 subjects that met the primary effectiveness endpoint. The following table (Table 22) shows the breakdown of the primary endpoint by its two components, pH normalization and at least 50% reduction in acid exposure from baseline. The middle column shows the results for 100 implanted subjects (i.e., the Treated group), while the last column provides a summary for the 96 subjects completing the 12 months of follow-up.

Table 22: Components of Primary Effectiveness Endpoint

Primary Efficacy Endpoint Component	% Successful (Number of Subjects/Total Subjects Implanted)	% Successful (Number of Subjects/Total Subjects Evaluated at Month 12)[1]
Normalization (≤4.5%)	56.0% (56/100)	58.3% (56/96)
≥50% reduction from baseline	61.0% (61/100)	63.5% (61/96)
Either normalization or ≥50% reduction	64.0% (64/100)	66.7% (64/96)

[1]Two subjects were withdrawn prior to 12 months, and two subjects at 12 months did not complete the pH portion

The eight subjects who met the primary endpoint but did not have normalization of their pH were evaluated to determine whether not achieving pH normalization was relevant. The majority of patients had improvement in their GERD symptoms and PPI usage. The following table (Table 23) shows the esophagitis status for these eight subjects as well.

Table 23: Esophagitis in Subjects with ≥ 50% Reduction but not Complete Normalization of pH

	Total Time pH<4			Esophagitis	
Subject	Baseline Total % Time	12M Total % Time	% Reduction	Baseline	12M
[redacted]	14.3	6.6	53.8	Grade A	None
[redacted]	18.5	8.2	55.7	None	None
[redacted]	25.4	6.6	74.0	Grade A	None
[redacted]	10.6	4.6	56.6	Grade B	Grade A
[redacted]	15.7	7.6	51.6	None	None

	Total Time pH<4			Esophagitis	
Subject	Baseline Total % Time	12M Total % Time	% Reduction	Baseline	12M
[redacted]	19.8	5.3	73.2	Grade A	None
[redacted]	24.7	7.4	70.0	None	None
[redacted]	25.3	8.3	67.2	None	None

Although not presented in Table 23, information on esophagitis for these eight subjects was evaluated.

- Subjects [redacted] and [redacted] went from no esophagitis at 12 months to Grade A esophagitis at 24 months.
- Subject [redacted] continued to have Grade A esophagitis at 24 months.

Secondary Endpoints

1. GERD-HRQL scores off GERD medications at baseline and 12 months. Subject-level success was defined as ≥ 50% reduction in total GERD-HRQL score at 12 months post implantation compared to baseline. The endpoint was met if the lower bound of a 97.5% confidence interval for the success rate was at least 60%.

The following table (Table 24) shows the percentage of patients successful in meeting this endpoint. Results are shown for both 12- and 24-month follow-up. Note that the lower confidence limits reported in the last column are both above the 60% success threshold.

Table 24: Secondary Endpoints GERD-HRQL Score at 12 and 24 Month Follow-up

Secondary Effectiveness Endpoint 12-Month Data	% Successful (Number of Subjects/Total)	Lower 97.5% Exact Binomial Confidence Limit
GERD-HRQL: ≥50% reduction	92.0% (92/100)	84.8%
	% Successful (Number of Subjects/Total Subjects Evaluated)	**Lower 97.5% Exact Binomial Confidence Limit**
GERD-HRQL: ≥50% reduction	93.3% (84/90)	86.1%

As shown in Table 24, the sponsor uses a denominator of 90 when reporting the 24-month success rate for the GERD-HRQL endpoint. This analysis is based on the 90 subjects completing follow-up through 24 months, ignoring the missing responses for subjects who were explanted or lost to follow-up. FDA believes that a more reasonable analysis would be based on the Treated group (including the 100 implanted subjects), as was done for the analyses at 12 months. Basing the 24-month GERD-HRQL analysis on the Treated group (and treating any missing responses as failures), the success rate is 84% (84/100), with a lower 97.5% confidence limit of 75.3%.

The following table (Table 25) provides a summary of the total GERD-HRQL scores at baseline, month 3, month 6, month 12, and month 24. The table also summarizes the reductions in GERD-HRQL scores from baseline.

Table 25: Summary of GERD-HRQL total scores by follow-up visit.

Visit	N	Mean (SD)	Minimum	Maximum
Baseline (On PPI)	100	12.0 (6.8)	0	28
Baseline (Off PPI)	100	26.6 (6.6)	11	47
Month 3*	98	4.3 (5.8)	0	35
Month 6*	98	4.8 (5.6)	0	31
Month 12*	95	3.8 (5.0)	0	30
Month 24*	90	4.3 (5.4)	0	27

*Scores recorded while subjects were off PPI medications.

Patient satisfaction was evaluated by visit (Table 26). At baseline no subject was "Satisfied" while off their PPIs, but by 12 months 95% of subjects had a "Satisfied" rating.

Table 26: Patient Satisfaction at Baseline and After Device Implantation

GERD-HRQL Satisfaction	Baseline Off PPI % (n/N)	Baseline On PPI % (n/N)	Month 12 % (n/N)	Month 24 % (n/N)
Satisfied	0.0% (0/100)	13.0% (13/100)	94.7% (90/95)	90.0% (81/90)
Neutral	5.0% (5/100)	21.0% (21/100)	2.1% (2/95)	6.7% (6/90)
Dissatisfied	95.0% (95/100)	66.0% (66/100)	3.2% (3/95)	3.3% (3/90)

Table 27 provides information on the percentage of subjects who met the secondary endpoint who did or did not meet the primary endpoint.

Table 27: Summary of Secondary Endpoints compared to the Primary Endpoint

Secondary Endpoints	Number of Subjects Meeting Endpoint	Primary Endpoint Success	Normalization of pH	≥50% Reduction (without Normalization)
GERD-HRQL	92%	61%	53%	8%
PPI Reduction	93%	62%	54%	8%
Success on both GERD-HRQL and PPI	89%	60%	52%	8%

2. PPI use at baseline and 12 months – Subject-level success was defined as reduction in PPI daily dose by ≥ 50% at 12 months post implantation compared to baseline. This endpoint was met if the lower bound of a 97.5% confidence interval for the success rate was at least 60%.

The following table (Table 28) shows the percentage of patients successful in having their PPI dosage reduced by at least 50%. Results are shown for both 12- and 24-month follow-up. Note that the lower confidence limits reported in the last column are both above the 60% success threshold.

Table 28: Secondary Effectiveness Endpoint, PPI Use

Secondary Effectiveness Endpoint 12-Month Data	% Successful (Number of Subjects/Total)	Lower 97.5% Exact Binomial Confidence Limit
PPI Use: ≥50% reduction in daily use	93.0% (93/100)	86.1%
24-Month Data	**% Successful (Number of Subjects/Total Subjects Evaluated)**	**Lower 97.5% Exact Binomial Confidence Limit**
PPI Use: ≥50% reduction in daily use	95.6% (86/90)	89.0%

The sponsor uses a denominator of 90 when reporting the 24-month success rate for the PPI dosage endpoint. This analysis is based on the 90 subjects completing follow-up through 24 months, ignoring the missing responses for subjects who were explanted or lost to follow-up. FDA believes that a more reasonable analysis would be based on the Treated group (including the 100 implanted subjects), as was done for the analyses at 12 months. Basing the 24-month PPI dosage analysis on the Treated group (and treating any missing responses as failures), the success rate is 86% (86/100), with a lower 97.5% confidence limit of 77.6%.

Table 29 shows the changes in frequency of PPI use at 12 and 24 months post implantation.

Table 29: Frequency of PPI use

PPI Use	Baseline (%) N=100	12 Month (%)[2] N=97	24 Month (%) N=89
None	0.0% (0/100)	88.7% (86/97)	86.7% (78/90)
PRN[1]	0.0% (0/100)	2.1% (2/97)	5.6% (5/90)
QD[1]	64.0% (64/100)	7.2% (7/97)	6.7% (6/90)
BID[1]	35.0% (35/100)	2.1% (2/97)	1.1% (1/90)
TID[1]	1.0% (1/100)	0.0% (0/97)	0.0% (0/90)

[1]**PRN**=as needed **QD**=once daily **BID**= twice daily **TID**=thrice daily

[2] One subject taking PPI for non-GERD related problems was excluded

3. Other parameters:

- Esophagitis:

Changes in esophagitis were measured at both 12 and 24 months (Table 30).

Table 30: Changes in Esophagitis at 12 and 24 months

Esophagitis Grade	Baseline % (n/N)	Month 12 % (n/N)	Month 24 % (n/N)
None	60.0% (60/100)	87.6% (85/97)	88.7% (79/89)
Grade A	22.0% (22/100)	10.3% (10/97)	7.9% (7/89)
Grade B	18.0% (18/100)	1.0% (1/97)	3.4% (3/89)
Grade C	0.0% (0/100)	0.0% (0/97)	0.0% (0/89)
Grade D	0.0% (0/100)	1.0% (1/97)	0.0% (0/89)

- Additional symptoms

There were some parameters on the Foregut questionnaire that were reported as improved from baseline such as regurgitation, heart burn, chest pain, cough, and pain.

- Manometry:

Manometry was measured at baseline and at 12 months (Table 31). There does not appear to be significant differences in values between baseline and 12 months. Mean % LES relaxation does appear to have slightly increased at 12 months as compared to baseline.

Table 31: Manometry Measurements at Baseline and 12 months

	Baseline			Month 12		
Parameter	N	Mean ± SD (Median)	Range	N	Mean ± SD (Median)	Range
LES resting tone (mmHg)	99	17.5±12.5 (15.4)	0.0, 70.0	93	22.5±13.7 (19.5)	3.0, 115.9
LES overall length (cm)	96	3.4±1.3 (3.5)	0.9, 7.7	93	3.4±1.4 (3.1)	0.6, 6.3
LES abdominal length (cm)	95	1.6±1.3 (1.5)	-1.5, 5.0	92	1.7±1.1 (2.0)	-1.0, 4.1
% liquid swallows effective	99	93.6±9.6 (100.0)	70.0, 100.0	93	85.3±21.2 (100.0)	20.0, 100.0

Table 27: Summary of Sec

Secondary Endpoints	Baseline			Month 12		
Parameter	N	Mean ± SD (Median)	Range	N	Mean ± SD (Median)	Range
LES residual pressure (mmHg)	94	3.8±4.5 (3.0)	-6.3, 22.2	93	7.3±6.6 (6.4)	-2.4, 24.8
GERD-HRQL		92%	61%		53%	8%
PPI Reduction		93%	62%		54%	8%
% LES relaxation	50	82.8±19.6 (88.0)	18.0, 103.0	38	84.5±12.8 (90.0)	50.0, 100.0
Success on both GERD-HRQL and PPI		89%	60%		52%	8%
Distal esophageal amplitude (mmHg)	100	78.1±27.4 (72.5)	35.0, 161.0	93	84.5±35.7 (81.3)	22.0, 192.1

Primary Endpoint

Normalization

Endpoint

2. PPI use at baseline and 12 months – Subject-level success was defined as reduction in PPI daily dose by ≥ 50% at 12 months post implantation compared to baseline. This endpoint was met if the lower bound of a 97.5% confidence interval for the success rate was at least 60%.

There were 32 subjects who had a hypotensive LES resting tone of < 10 mmHg at baseline. At 12 months:

- Of the 31 evaluated subjects who had a hypotensive LES at baseline, three remained hypotensive.
- 15 of 93 subjects had <70% effective swallows, and four subjects had distal esophageal amplitude <35 mmHg.
- One subject was reported to have ongoing complaints of dysphagia and abnormal motility (defined as <70% effective swallows and/or distal amplitude <35 mmHg).

The following table (Table 28) shows the percentage of patients successful in having their PPI dosage reduced by at least 50%. Results are shown for both 12- and 24-month follow-up. Note that the lower confidence limits reported in the last column are both above the 60% success threshold.

Table 28: Secondary Effectiveness Endpoint, PPI Use

Secondary Effectiveness Endpoint 12-Month Data	% Successful (Number of Subjects/Total)	Lower 97.5% Exact Binomial Confidence Limit
PPI Use: ≥50% reduction in daily use	93.0% (93/100)	86.1%
24-Month Data	**% Successful (Number of Subjects/Total Subjects Evaluated)**	**Lower 97.5% Exact Binomial Confidence Limit**
PPI Use: ≥50% reduction in daily use	95.6% (86/90)	89.0%

Information on the three subjects who continued to have a hypotensive LES is presented in Table 32.

The sponsor uses a denominator of 90 when reporting the 24-month success rate for the PPI dosage endpoint. This analysis is based on the 90 subjects completing follow-up through 24 months, ignoring the missing responses for subjects who were explanted or lost to follow-up. FDA believes that a more reasonable analysis would be based on the Treated group (including the 100 implanted subjects), as was done for the analyses at 12 months. Basing the 24-month PPI dosage analysis on the Treated group (and treating any missing responses as failures), the success rate is 86% (86/100), with a lower 97.5% confidence limit of 77.6%.

Table 29 shows the changes in frequency of PPI use at 12 and 24 months post implantation.

Table 32: Subjects with Hypotensive LES at Baseline and 12 months

Subject 3-004-001						
Subject ID	**Total % Time pH <4**	**Esophagitis LA Grade**	**Overall LES Length (cm)**	**LES Resting Tone (mmHG)**	**Total GERD-HRQL Score**	**PPI Use**
Baseline	13.2	None	ND	6.0	28	20 years
3 Months					6	None
6 Months					9	None
12 Months	9.0	None		9.0	2	None
Subject 03-004-002						
Subject ID	**Total % Time pH <4**	**Esophagitis LA Grade**	**LES Overall Length (cm)**	**LES Resting Tone (mmHG)**	**Total GERD-HRQL Score**	**PPI Use**
Baseline	10.1	None	ND	7.0	27	3 years
3 Months					0	None
6 Months					0	None
12 Months	1.7	None	3	7.0	0	None
Subject 03-008-007						
Subject ID	**Total % Time pH <4**	**Esophagitis LA Grade**	**Overall LES Length (cm)**	**LES Resting Tone (mmHG)**	**Total GERD-HRQL Score**	**PPI Use**
Baseline	8.3	None	3.5	7.5	25	3 years
3 Months					0	None
6 Months					0	None
12 Months	16.9	None	2.5	7.2	2	None

It is noted that for two of these patients the DeMeester score was greater than 14.7. in addition, for [redacted] grade A esophagitis was present at 24 months.

Protocol Deviations

There were a several protocol deviations involving subjects completing the follow up questionnaire while being on GERD medications. These subjects were asked to recall symptoms off GERD medications. This method may be inaccurate and improvement in symptoms may indeed be due to medication, falsely elevating device effect. This reinforces the concern of relying solely on subjective data at the 24 month time point.

Post-hoc subgroup analyses

As response rates for the primary effectiveness appeared to differ according to baseline hernia status and gender, the sponsor performed post-hoc subgroup analyses that were not pre-specified in the study protocol.

Analysis of effectiveness by baseline hernia status (Table 33) showed:

Table 29: Frequency of PPI use

PPI Use	Baseline (%) N=100	12 Month (%)[2] N=97	24 Month (%) N=90
None	0.0% (0/100)	88.7% (86/97)	86.7% (78/90)
PRN[1]	0.0% (0/100)	2.1% (2/97)	3.3% (3/90)
QD[1]	64.0% (64/100)	7.2% (7/97)	6.7% (6/90)
BID[1]	35.0% (35/100)	2.1% (2/97)	1.1% (1/90)
TID[1]	1.0% (1/100)	0.0% (0/97)	0.0% (0/90)

[1]PRN=as needed QD=once daily BID= twice daily TID=thrice daily
[2] One subject taking PPI for non-GERD related problems was excluded

The following table (Table 33) provides a breakdown of primary and secondary effectiveness endpoints for subjects based on their baseline hernia status:

Table 33: Primary and Secondary Effectiveness Endpoints Based on Hernia Status

	Number of subjects	% with primary endpoint success	% with success on secondary GERD-HRQL endpoint	% with success on secondary PPI endpoint
Hiatal hernia not repaired, still present at 12 months	4	25.0% (1)	75.0% (3)	100.0% (4)
Hiatal hernia not repaired, absent at 12 months	21	42.9% (9)	95.2% (20)	95.2%
Hiatal hernia repaired with baseline hernia present	30	66.7% (20)	100.0% (30)	96.7 (29)
No hiatal hernia at baseline[2]	44	77.3% (34)	88.6%(39)	90.9% (40)

[1]Does not include the 4 subjects with a hernia repair noted at implant but had a baseline hernia size of 0
[2]Three of these subjects are ITT failures due to missing pH evaluation at 12 months.
Note: One subject with an unrepaired hernia at baseline was not evaluated for the presence of a hernia at 12 months and therefore does not fall into any of the above categories.

- In the 44 patients with no hernia, there was a 77% (34/44) success rate for the primary endpoint.
- In the 30 patients who had a hernia repaired, the success rate for the primary endpoint was 67% (20/30).
- In the 26 patients who had a hernia that was not repaired, the success rate for the primary endpoint was 39% (10/26).
- It is noted that in 21 of the 26 patients who had an unrepaired hernia, no hernia was seen at the 12-month follow up.

3. Other parameters:

- Esophagitis:

Changes in esophagitis were measured at both 12 and 24 months (Table 30).

Table 30: Changes in Esophagitis at 12 and 24 months

Esophagitis Grade	Baseline % (n/N)	Month 12 % (n/N)	Month 24 % (n/N)
None	60.0% (60/100)	87.6% (85/97)	88.7% (79/89)
Grade A	22.0% (22/100)	10.3% (10/97)	7.9% (7/89)
Grade B	18.0% (18/100)	1.0% (1/97)	3.4% (3/89)
Grade C	0.0% (0/100)	0.0% (0/97)	0.0% (0/89)
Grade D	0.0% (0/100)	1.0% (1/97)	0.0% (0/89)

- Additional symptoms

There were some parameters on the Foregut questionnaire that were reported as improved from baseline such as regurgitation, heart burn, chest pain, cough, and pain.

- Manometry:

Manometry was measured at baseline and at 12 months (Table 31). There does not appear to be significant differences in values between baseline and 12 months. Mean %LES relaxation does appear to have slightly increased at 12 months as compared to baseline.

Table 31: Manometry Measurements at Baseline and 12 months

Parameter	Baseline N	Baseline Mean ± SD (Median)	Baseline Range	Month 12 N	Month 12 Mean ± SD (Median)	Month 12 Range
LES resting tone (mmHg)	99	17.5±12.5 (15.4)	0.0, 70.0	93	22.5±13.7 (19.5)	3.0, 115.9
LES overall length (cm)	96	3.4±1.3 (3.5)	0.9, 7.7	93	3.4±1.4 (3.1)	0.6, 6.3
LES abdominal length (cm)	95	1.6±1.3 (1.5)	-1.5, 5.0	92	1.7±1.1 (2.0)	-1.0, 4.1
% liquid swallows effective	99	93.6±9.6 (100.0)	70.0, 100.0	93	85.3±21.2 (100.0)	20.0, 100.0

Analysis by gender

A subgroup analysis was also performed by gender. The success rates for the primary and secondary effectiveness endpoints are presented in Table 34. The observed success rates for females are generally higher than for males.

The subjects were not assigned to an intervention group of hernia repair or no hernia repair prior to the implantation procedure. The decision to perform a hernia repair was made intra-operatively by the implanting surgeon when direct visualization was available to fully assess the presence and extent of a hernia and the surrounding anatomy. The decision to repair a hiatal hernia was based on the implanting surgeon's clinical judgment and the anatomy of the hiatus.

Table 34: Secondary Endpoints by Gender

Endpoint	Males (n=52)	Females (n=48)	All Subjects (n=100)
Primary			
pH Normalization >50% reduction	51.9% (27)	77.1% (37)	64.0% (64)
Secondary			
GERD-HRQL >50% reduction in total score	88.5% (46)	95.8% (46)	92.0% (92)
PPI Use >50% reduction in average daily use	92.3% (48)	93.8% (45)	93.0% (93)

The primary and secondary endpoints were further evaluated in the subgroups defined by the cross-classification of gender and baseline hernia status (Table 35). The observed success rate for each subgroup is shown in the following table. Females generally had higher success rates than males within each classification for hernia status. The group with the lowest success rate was found to be males with a hernia present at baseline that was not repaired (3/15; 20%).

Table 35: Primary Effectiveness Endpoint by Gender and Hernia Status at Baseline

Hernia Status at Baseline	Male % pH Success (n/N)	Female % pH Success (n/N)
None	69.6% (16/23)	85.7% (18/21)
Repair	57.1% (8/14)	75.0% (12/16)
No Repair	20.0% (3/15)	63.6% (7/11)

FDA Comments on Effectiveness

After review of the clinical data, the FDA has the following comments.

1. Regarding the primary effectiveness endpoint for the clinical study was at least 60% of the subjects implanted with the LINX device had to achieve at least a 50% reduction in total acid exposure of the esophagus at 12 months; the study did not meet this endpoint. Although a total of 64 out of the 100 implanted patients achieved success, the data failed to reject the pre-specified null hypothesis for primary effectiveness at a p-value of 0.24.

2. Esophageal pH testing was not repeated at 24 months. It is reported that this was due to the test being uncomfortable, logistically more difficult, and not considered critical to the continued monitoring of safety and effectiveness in light of the many evaluations that were

performed. The FDA questions why a BRAVO capsule could not have been placed at the time of the endoscopy at the pre-scheduled 24 month follow-up visit. Since the capsule would have been placed endoscopically, patients should not have felt much discomfort. Most importantly, since the ambulatory 24-hour esophageal pH monitoring has become the "gold standard" for the diagnosis of GERD[1], pH testing would have been the most critical to determining device effectiveness.

3. Reporting on GERD symptoms and PPI usage is subjective and could be affected by the fact that both subjects and physicians knew that the subject was treated with the device. In addition, since there was no blinding, subjects may have tended to be optimistic in reporting improvements and physicians may have been influenced in their decisions to change PPI dosage. In light of the drawbacks of subject self-reporting and the lack of objective measures at 24 months, whether the results are clinically significant enough to warrant approval should be discussed.

4. Regarding the analysis of the effectiveness of the LINX System as assessed by the presence of a hiatal hernia at baseline:

    a. In subjects who continued to have a hernia, success in meeting the primary endpoint was the lowest.

    b. In subjects with a hernia at baseline, but the hernia was not seen at 12 months (n=21), the percentage of subjects meeting the primary endpoint was approximately 18% higher compared to the four subjects who did not have their hernia repaired but the hernia was still observed at 12 months. Possible reasons for not being able to visualize the hernia included such things as difficult to detect by endoscopy, anatomy may present differently due to dissections and healing of tissue around the gastroesophageal junction, were self-corrected by the surgery and placement of the LINX device.

    c. In subjects that had a hernia that was actively repaired (n=30), the percentage of subjects meeting the primary endpoint was approximately 24% higher compared to subjects that did not have their hernia repaired but the hernia was not seen at 12 months (n=21) .

    d. Since all hernias were small, it is unclear why the 21 subjects who did not have the hernia repaired but the hernia was not observed at 12 months, had a much lower success rate (24%) compared to subjects who did have their hernia repaired (42.9% vs. 66.7%)

    e. Based on the results of the study, the sponsor is recommending that patients who have a hiatal hernia should have it repaired at the time of device placement. Overall, there was a 28% difference in success rate between subjects that had their hernia repaired and subjects that did not. This raises the question of whether the hernia repair itself had any part in reducing esophageal acid exposure. Since the subgroup analyses were not pre-specified and type I error was not controlled in these analyses, whether a formal conclusion regarding small hernia repair based on a post-hoc analysis, should be discussed.

5. The difference in pH normalization between males and females appears to be significant (77.1% success vs 51.9% success), but is unclear as to why.

6. The sponsor included the Foregut questionnaire as an assessment tool; it is noted that there are no literature references to support the validation of this assessment tool.

References

1. Streets, C.G. *et al*. (2003) Ambulatory 24-hour Esophageal pH Monitoring Why, When, and What to Do. *J Clin Gastroentero;* 37(1):14–22.

2. Oelschlager, B.K., Eubanks, T.R., Pellegrini, C.A., Townsend: Sabiston Textbook of Surgery, (18th ed.) Saunders. 2007. Chapter 42- Hiatal Hernia and Gastroesophageal Reflux Disease

3. Smith, C.D. (2009) Surgical Therapy for Gastroesophageal Reflux Disease: Indications, Evaluation, and Procedures. *Gastrointest Endoscopy Clin N Am;* 19: 35–48

Marketing Experience

The LINX Reflux Management System is currently marketed outside in Europe. As of November 2011, there have 98 implants in Europe. One patient had complaints of odynophagia following the LINX procedure and had the device removed with fundoplication performed. This occurred approximately seven months following the implant and the odynophagia was reported to have resolved without sequelae. One patient had dysphagia and underwent dilation with reported resolution of symptoms.

IX. Post-Approval Study Considerations

NOTE TO PANELISTS: FDA's inclusion of a section/discussion on a Post-Approval study (PAS) in this executive summary should not be interpreted to mean that FDA has made a decision on the approvability of this PMA. The presence of post-approval study plans or commitments does not in any way alter the requirements for premarket approval. A recommendation from the Panel on whether the data demonstrates reasonable assurance on device safety and effectiveness must be based solely on the premarket data. The issues noted below are FDA's comments regarding potential post-approval studies.

Overview of Proposed Post-Approval Studies

The applicant is proposing to conduct two post-approval studies for the current PMA: an Extended 5-year Follow-Up of the PMA cohort as well as a 3-year New Enrollment study to evaluate real world effectiveness and safety.

1. Extended Follow-up of PMA Cohort

Study Component	Description	Additional Details
Study Questions	The purpose of the study is to evaluate the long-term safety and effectiveness of the LINX device in the treatment of Gastroesophageal Reflux Disease (GERD).	
Study Design	The study is a prospective, multicenter, single arm clinical study that will be conducted in the United States and Europe.	
Study Population	Subjects ages ≥ 18, or Age of Majority according to Law in states or countries where 18 is considered a minor, and < 75 years seeking intervention for GERD who meet the study inclusion / exclusion criteria are eligible for this study.	Subjects were enrolled in the pre-market phase and are at least partially responsive to medical therapy (proton pump inhibitors) for their GERD symptoms and have tested positive (abnormal) in esophageal pH testing.
Sample Size (Patients and Sites)	This clinical evaluation will be conducted at up to twenty (20) U.S. investigational Centers and additional European Centers that participated in the premarket study. Investigators were selected among surgeons with experience performing anti-reflux laparoscopic procedures. The study subjects consist of a 100 subjects that were implanted with the device from the premarket study.	No precision or power analysis was provided for the long-term safety and effectiveness endpoints. Additionally, there is no description of the number of patients that will be followed.
Endpoints *1. Long-Term* *a. Safety* *b. Effectiveness* *Performance*	 The long-term safety endpoint is the rate of occurrence for serious device and procedure related adverse events. The long-term safety endpoint will be assessed by reporting all adverse events and by estimating the rate of serious device- and procedure-related adverse events through 60 months post implantation. Subjects will be followed to 60 months post-implant to assess the long term effectiveness of the LINX device. The subject's baseline GERD-HRQL (Health Related Quality of Life) score will serve as the control and be compared to the subject's GERD-HRQL at 60 months post implantation. A subject will have a 50% reduction in total GERD-HRQL scores. Subject's average daily dose of proton pump inhibitors (PPI) will be evaluated. The subject's baseline average daily dosage will serve as the control and be compared to the subject's average daily dosage 12 months post-procedure. A subject will reduce their average daily PPI dosage ≥50%	

Follow-up Visits and Length of Follow-up	Study duration is approximately 6 years, includes time for enrollment and completion of 60 month follow-up. Assessment will happen at: 24-month, 36-month, 48-month, and 60-month follow up.
Enrollment Plan and Follow-up Measures	The study is an extended follow-up of the pre-market study, so no new enrollment will take place. No plans to retain subjects and keep a high follow up rate are included in the protocol
Statistical Plan	No specific statistical analysis plan is included.
Timeline for Study Implementation	No specific timeline with dates is included.

2. New Enrollment Study

Study Component	Description
Study Objectives	The primary safety and effectiveness objectives are: ▪ To provide long-term safety information on subjects implanted with the LINX device ▪ To demonstrate long-term clinical effectiveness in the reduction of GERD related symptoms in subjects receiving the LINX implant
Study Design	The LINX Post Approval Study is a prospective, multi-center, single arm observational study with subjects serving as their own control for assessment of the long-term safety and effectiveness of the LINX Reflux Management System.
Study Hypotheses	The primary effectiveness objective will be successful reduction of ≥ 50% in the total GERD-HRQL score at 36 months as compared to baseline. The primary effectiveness objective will be analyzed according to the following hypotheses: H0: $\Pi \leq 60\%$ HA: $\Pi > 60\%$ where Π is the percent of subjects with a reduction of ≥ 50% in the total GERD-HRQL score at 36 months as compared to baseline. The percent of subjects with a successful reduction in GERD-HRQL will be compared to the performance goal of 60% using a one-sided, binomial exact test.
Study Population	Newly enrolled subjects who meet the following inclusion/exclusion criteria: Inclusion Criteria ▪ Subject has provided written informed consent to participate. ▪ Subject is an appropriate candidate for LINX implant as

	specified in the Indications and Contraindications from the LINX's Instructions for Use (IFU) ▪ Subject has indicated a willingness to comply with study requirements for the specified follow-up duration. Exclusion Criteria ▪ Known circumstances that would make it unlikely for an individual to complete the three year follow-up (e.g. life expectancy <3 years)
Sample Size (Patients and Sites)	Up to 25 sites will participate and a maximum of 200 subjects will be implanted. The required sample size was calculated using the following assumptions: ▪ Type I error = 2.5% ▪ Assumed success rate (at least 50% improvement in GERD score) = 80% ▪ Power = 90% Under these assumptions, a minimum of 72 subjects implanted with the LINX device and followed to 36 months are required. The study will enroll up to 200 subjects. Up to 25 sites will participate.
Endpoints	Specific endpoints and a schedule of data collection are presented in Table 1 below.
Follow-up Visits and Length of Follow-up	3-year follow up: the study will included pre-operative, surgery, 6-week to 6month, 12-month, 24-month and 36-month follow up evaluations.
Enrollment Plan and Follow-up Measures	No specific enrollment plan is reported. No follow up plans to retain subjects and keep a high follow up rate are included in the protocol.
Statistical Plan	General Analysis Methods All study demographics and study outcomes will be summarized with basic summary statistics which will include the number and percent for categorical parameters and the mean, standard deviation, median and range for continuous parameters. Associated confidence limits will also be calculated. Primary Safety and Effectiveness Outcomes The primary safety endpoint of serious device related adverse events will be summarized overall and by type of event. All adverse events will be summarized overall and by type of event, seriousness and intervention required. The primary effectiveness objective will be summarized as the number and percent of subjects assessed at 36 months follow-up who

	demonstrate a ≥ 50% reduction in the total GERD-HRQL score from baseline. The associated 95% binomial exact confidence limits will also be calculated. Handling of Missing Data Subjects who withdraw from the study seeking alternative treatment will be included in the primary effectiveness analysis as failures. Sensitivity analyses will be conducted to assess the impact of early withdrawal and missing data on the primary analyses. These may include a tipping point analysis to determine the necessary failure rate in the subjects with missing endpoint data to change the study outcome, last observation carry forward (LOCF) and multiple imputation analysis.
Timeline for Study Implementation	A draft timeline is included without no specific dates for study milestones

Data Collection (Endpoints), Follow-up Visits and Length of Follow-up for Newly Enrolled Study

Table 1. Schedule of Data Collection

Pre-Operative	Surgery	6-weeks – 6-months	12-months	24-months	36-months	Data Collected
R						Demographics
R						Baseline Screening
R[1]						Pre-surgery and GERD Questionnaire[3]
	R					Surgery/Discharge Data
		O				Abdominal/Chest X-ray
			R[2]	**R**[2]	**R**[2]	Post-surgery and GERD Questionnaire[3]
			R	**R**	**R**	Healthcare Resource Utilization
			R	**R**	**R**	GERD Medications
	R		**R**	**R**	**R**	Serious Adverse Events

* Visit window is +/- 60 days from implant anniversary date

R=Required
O=Optional, not required
[1]=On GERD medications
[2]=May be on or off GERD medications based on subjects current medications
[3]= Questionnaire completed by subject, incorporates the GERD-HRQL symptom severity instrument[5]

FDA Assessment of PAS Proposals

Extended Follow-up Study
The protocol still lacks important components such as study questions, formal statistical tests for the long-term hypotheses, number of patients to be followed, precision and power calculations based on such safety and effectiveness hypotheses, plan to minimize loss to follow up, statistical analysis plan, detailed study timeline and reporting requirements (interim and final reports).

FDA believes it would be critical that esophageal pH measurement is performed as the primary effectiveness measure at all follow up visits as esophageal pH measurements are considered the gold standard and ≥ 50% reduction in the total GERD-HRQL score from baseline has poor sensitivity.

New Enrollment Study
The protocol still lacks important components such as study questions, recruitment strategy and enrollment plan, plan to minimize follow up, a detailed study timeline with dates and reporting requirements (interim and final reports).Furthermore, some of the presented components of the PAS protocol are in need of further development, such as: a more detailed description of study population, statistical analyses with testable hypotheses.

FDA believes the follow up time of the study should be at least 5 years, not 3 as currently planned, since this is a permanently implanted device. FDA believes it would be critical that esophageal pH measurement is performed as the primary effectiveness measure at all follow up visits as esophageal pH measurements are considered the gold standard and ≥ 50% reduction in the total GERD-HRQL score from baseline has poor sensitivity.

Questions to Panel

The Panel will be asked to comment on the need for a PAS (should the application be approved). Should a PAS be recommended, the Panel will be asked to comment on various elements of the proposed study design. Specifically, the Panel will be asked to discuss the following:

1. Should the device be approved, the applicant is proposing two Post-Approval Studies to monitor postmarket safety and effectiveness. The first study is an extended follow-up of the premarket cohort. Please discuss the following:

    a. In the premarket study the primary effectiveness endpoint was esophageal pH, but in the protocol of the extended follow up study, the applicant has proposed to use reduction in the total GERD-HRQL score from baseline as the primary long-term effectiveness outcome. Please discuss the appropriateness of this proposed measure, and whether measurement of esophageal pH would be needed.

    b. The sponsor is proposing to study serious device and procedure related adverse events in the extended follow up study. Please discuss if there are additional adverse events that need to be studied postmarket.

c. There are no plans to study specific subgroups according to disease type in the extended follow up study. Please discuss whether the study should consider subgroups analyses of specific disease types?

2. Should the device be approved, the applicant is also proposing a new enrollment Post-Approval Study to monitor postmarket safety and effectiveness. Please discuss the following:

   a. The sponsor has proposed a study duration of 3 years. Please discuss whether a 3-year follow up is sufficient to study real world long-term safety and effectiveness of the device.

   b. In the premarket study the primary effectiveness endpoint was esophageal pH, but in the protocol of the new enrollment study, the applicant has proposed to use reduction in the total GERD-HRQL score from baseline as the primary effectiveness outcome. Please discuss the appropriateness of this proposed measure, and whether measurement of esophageal pH would be needed.

   c. The sponsor is proposing to study serious device and procedure related adverse events in the new enrollment study. Please discuss if there are additional adverse events that need to be studied postmarket.

   d. There are no plans to study specific subgroups according to disease type in the new enrollment study. Please discuss whether the study should consider subgroups analyses of specific disease types?

X. Training

The sponsor intends to institute a required training program for new users to educate them on patient selection, device implantation and post-procedural care of patients treated with the LINX System. This program will focus on the safe and appropriate use of the LINX Reflux Management System in the intended patient population and will provide physicians with the necessary information and resources to counsel patients on the potential risks and benefits of treatment with the LINX System so an informed decision can be made by the patient.

The sponsor also intends to establish a Training Advisory Panel of at least three to five gastroenterologists and surgeons experienced with GERD and the LINX System who can provide guidance on and review of the training program prior to and following its implementation.

XI. Conclusions

The data presented in the PMA supplement characterize the safety and effectiveness of the LINX™ Reflux Management System

The sponsor has drawn the following conclusions from their analysis of the data:

- The LINX System is intended to address the unmet need for a treatment option in patients opting for life-long PPI therapy or surgery.

- The data presented characterize the safety and effectiveness of the LINX device in subjects with abnormal pH testing who continue to have GERD symptoms despite PPI therapy.

- The sponsor states the following from the analysis of their data:

    - 64% of the subjects achieved the primary endpoint for reduced esophageal acid exposure. Even though the lower bound of the confidence interval was 54%, the observed improvements in symptoms, PPI use, and overall safety validates the success of the clinical investigation.

    - The lower bound confidence intervals showed 85% of study subjects successfully achieved the endpoint for reduction in symptoms and 86% successfully achieved the endpoint for reduction in PPI use, providing evidence of clinical benefit.

    - There were no intra-operative complications, no new or unknown risks, and a serious adverse event rate no greater than what is expected following any anti-reflux surgery.

- After review of the data, the FDA agrees that there was evidence of pH normalization as well as improvement in GERD symptoms and PPI use in several subjects. However, the following issues still exist:

    - The study did not meet the primary endpoint

    - Beyond the 1 year time point, pH testing was not performed and improvement was assessed through quality of life instruments which are dependent on accurate subject reporting.

    - There was a 28% difference in success rate between those that had their hernia repaired and those that did not raising the question of success in reducing esophageal exposure being from hernia repair versus the device.

    - In some cases, dysphagia was prolonged, several subjects required esophageal dilations, and some subjects wished to have the device explanted.

Therefore, there are several issues that the FDA would like the Advisory panel to comment on.

- The primary effectiveness endpoint of normalized or improved pH (<4 for ≤4.5% of total monitoring time) by at least 50% in total distal acid exposure, in at least 60% of subjects as indicated by the lower bound of a 97.5% confidence interval for the observed success rate was not met. Although a total of 64 out of the 100 implanted patients achieved success, the data failed to reject the pre-specified null hypothesis for primary effectiveness at a p-value of 0.24. Please discuss whether the data support the effectiveness of the LINX device.

- Regarding the durability of the effectiveness of the LINX Reflux Management System, the 24 month evaluations did not include assessment of the objective measure of esophageal pH. Please discuss whether there are adequate data to support the claim that the effectiveness of the device is sustained based only on subjective data such as GERD-HRQL scores and reduction in medication use.

- Although not pre-specified in the protocol, the sponsor evaluated the effectiveness results based on post-hoc subgroup analysis for the presence of a hiatal hernia. This analysis concluded that a hernia repair at the time of device placement achieved a success rate of 67% while subjects who did not have their hernia repaired achieved only a 39% success rate. Please discuss whether the data are adequate to justify the conclusion that the hernia repair with implantation of the LINX device was the reason for the 67% success rate rather than being due to a hernia repair alone.

- The data shows that at 12 months there were a total of 162 adverse events reported in 76% of the subjects enrolled in the study. Dysphagia appears to be a significant complication; there were 76 events of dysphagia reported in 68% of the subjects and 11% of the subjects reported ongoing dysphagia. Eighteen (18) patients underwent esophageal dilatation and 10 continued to have dysphagia at 24 months. Please discuss whether there is a clinical benefit to device use given the potential risk of dysphagia requiring either dilatation or device removal.