SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implant, Gastroesophageal Reflux

Device Trade Name: LINX ™ Reflux Management System

Applicant's Name and Address: Torax Medical, Inc
4188 Lexington Avenue North
Shoreview, Minnesota 55126

Date of Panel Recommendation: January 11, 2012

Premarket Approval Application (PMA) Number: P100049

Date of FDA Notice of Approval: March 22, 2012

Expedited: Not applicable

II. INDICATIONS FOR USE

The LINX™ Reflux Management System is indicated for patients diagnosed with Gastroesophageal Reflux Disease (GERD) as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite maximum medical therapy for the treatment of reflux.

III. CONTRAINDICATIONS

Do not implant the LINX™ Reflux Management System in patients with suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the LINX™ Reflux Management System labeling.

V. DEVICE DESCRIPTION

The LINX™ Reflux Management System (LINX device) 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) and minimize or eliminate GERD related symptoms.

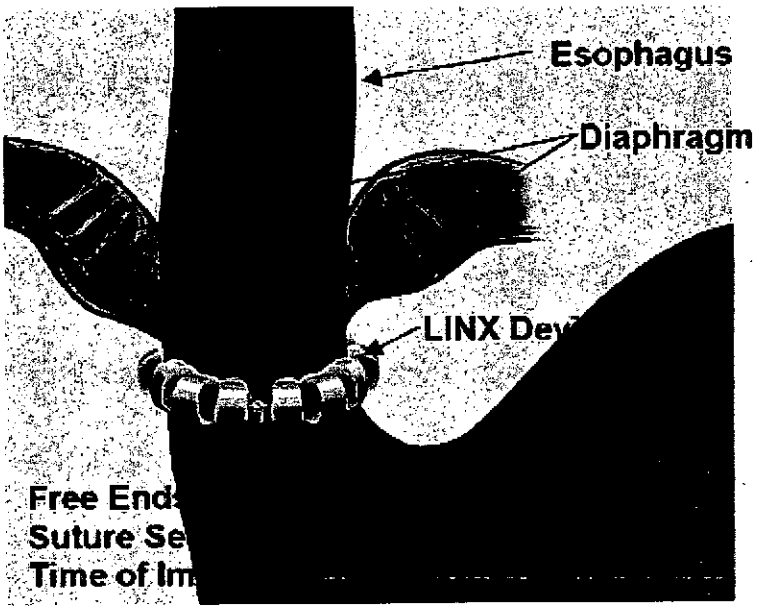


Figure 1: Illustration of the LINX Device on the Esophagus

The LINX™ Reflux Management System is comprised of two (2) 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 strength to help keep the LES 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.

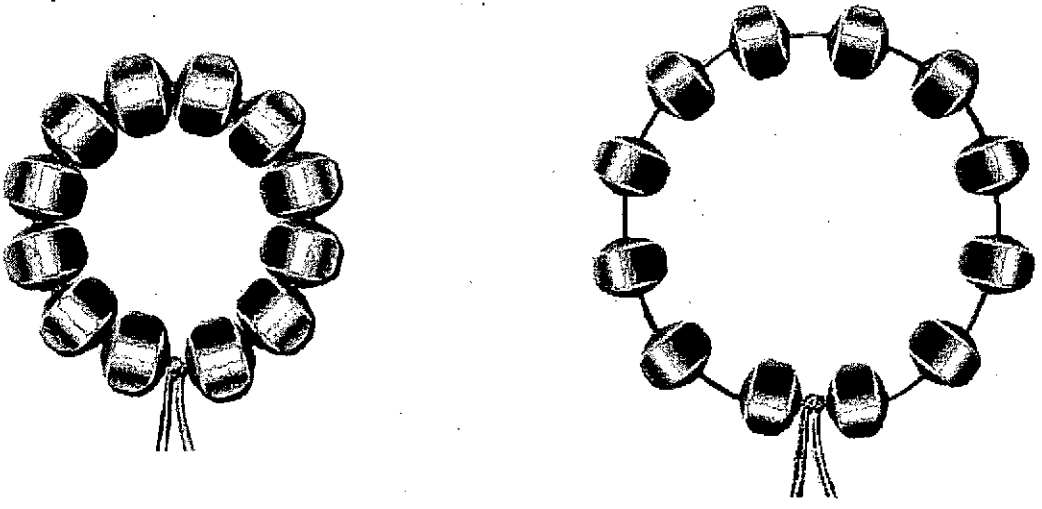


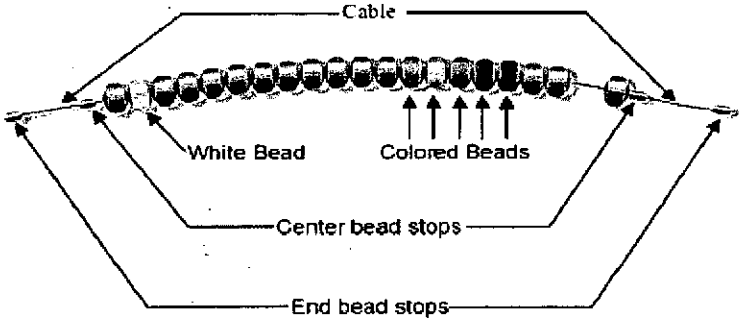
Figure 2: LINX Reflux Management System Implant (closed and opened)

The LINX device is available in multiple sizes to accommodate variation in esophagus size (Table 1). The length is based on the number of beads. The sizes are denoted by the model number (e.g., LS 12 = 12 bead implant).

Table 1: Circumference Calculation for the LINX Device

Device Size	Internal Diameter of Closed Device	Calculated Internal Circumference of Closed Device	Esophagus Diameter Range
10 bead	0.43 inches	1.34 inches	0.39 – 0.43 inches
11 bead	0.47 inches	1.48 inches	0.43 – 0.47 inches
12 bead	0.52 inches	1.62 inches	0.47 – 0.52 inches
13 bead	0.56 inches	1.76 inches	0.52 – 0.56 inches
14 bead	0.60 inches	1.89 inches	0.56 – 0.60 inches
15 bead	0.65 inches	2.03 inches	0.60 – 0.65 inches
16 bead	0.69 inches	2.17 inches	0.65 – 0.69 inches
17 bead	0.73 inches	2.31 inches	0.69 – 0.73 inches
18 bead	0.78 inches	2.44 inches	0.73 – 0.78 inches

The LINX Sizing Tool (Figure 3) is used at the time of implant to assist the physician in choosing an appropriately sized LINX 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 and the colored bead that meets the white bead determines the appropriate sized implant device.



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.

Figure 3: LINX Reflux Management System 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 device can be placed laparoscopically through a port with a minimum internal diameter of 10mm or directly via laparotomy. The surgical procedure is similar to a Nissen fundoplication in that it can be done laparoscopically; however, 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).

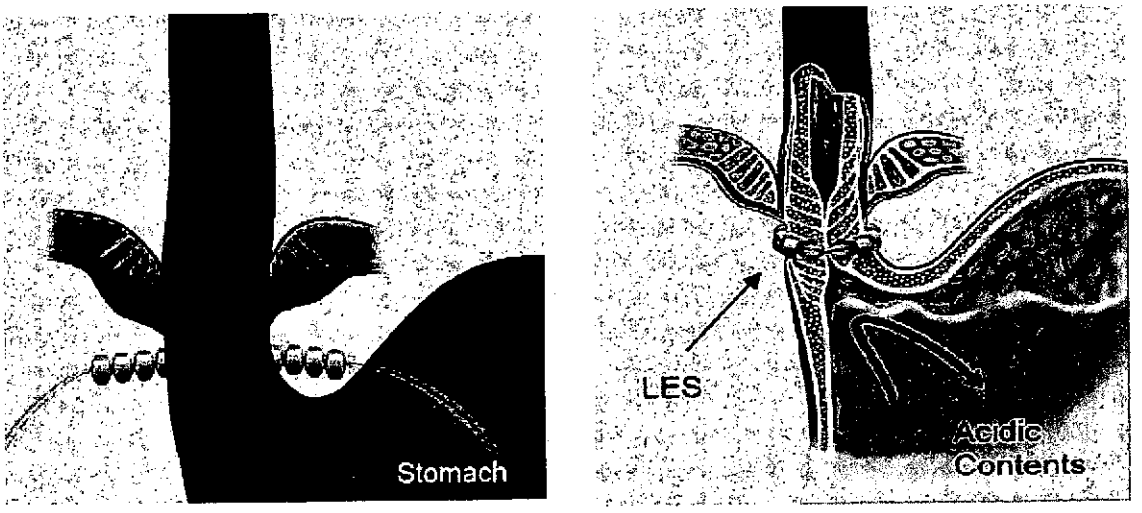


Figure 4: LINX Encircling the Esophagus to Prevent Reflux

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.

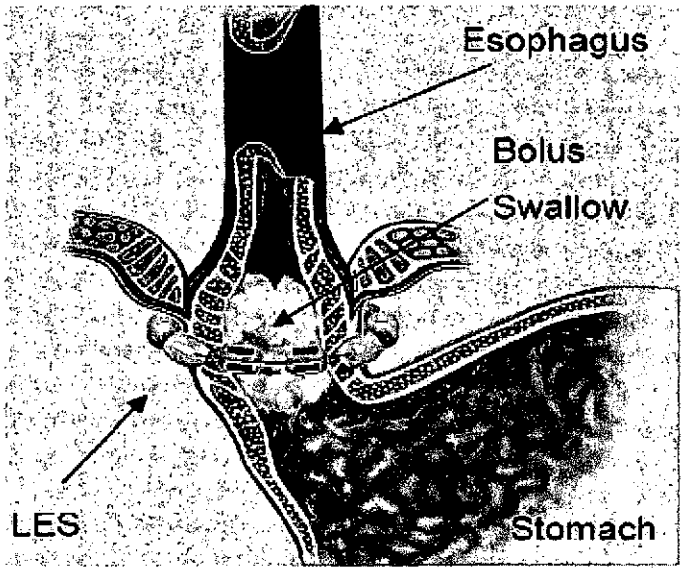


Figure 5: Device Actuation During Swallowing

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of GERD. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

Lifestyle/Dietary Modifications
Simple lifestyle or dietary modifications are often recommended as part of the initial therapy for mild GERD symptoms and may include:

- Elevating the head of the bed;
- Weight loss;
- Avoiding alcohol, tobacco, caffeine, acidic foods/beverages; and
- Not eating prior to laying down or going to bed

Acid-Suppression Therapy (Pharmacological)
Subjects who fail to respond to lifestyle/dietary modifications are often treated with acid-suppressive or neutralizing medications, typically classified into four (4) broad categories:

- Antacids;
- H_2 Receptor Antagonists (H_2RA); and
- Proton Pump Inhibitors (PPIs)
- Other

Surgical Therapy
Several different surgical procedures which use portions of the stomach to wrap around the esophagus are performed to treat GERD, including the Nissen fundoplication, Belsey operation, and Hill procedure. Additionally, endoscopic procedures that utilize ablation technology and plication devices have emerged to treat GERD.

VII. MARKETING HISTORY

The LINX™ Reflux Management System obtained CE mark in 2008 and has been marketed in European Union since that time. The LINX™ has not been withdrawn from the market in any country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the LINX™ Reflux Management System.

Adverse events that may result from use of the LINX™ Reflux Management System are both those commonly associated with general surgical procedures, as well as those associated with the device specifically.

Potential adverse events associated with laparoscopic surgery and anesthesia include adverse reaction to anesthesia (headache, muscle pain, nausea), anaphylaxis, cardiac arrest, death, diarrhea, fever, hypotension, hypoxemia, infection, myocardial infarction, perforation, pneumonia, pulmonary embolism, respiratory distress, and thrombophlebitis. Other risks reported after anti-reflux surgery procedures include bloating, nausea, dysphagia, odynophagia, retching, and vomiting.

Risks associated specifically with the LINX ™Reflux Management System include achalasia, bleeding, death, decreased appetite, device erosion, device explant/re-operation, device failure, device migration (device does not appear to be at implant site), diarrhea, dysphagia, early satiety, esophageal spasms, flatulence, food impaction, hiccups, inability to belch or vomit, increased belching, infection, impaired gastric motility, injury to the esophagus, spleen, or stomach, nausea, odynophagia, organ damage caused by device migration, pain, peritonitis, pneumothorax, regurgitation, stomach bloating, vomiting, weight loss, and worsening of preoperative symptoms (including, but not limited to dysphagia or heartburn).

The LINX™ Reflux Management System is intended to be a long-term implant, and may need to be either explanted or replaced. For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

The integrity and performance of the LINX Reflux Management System was evaluated through the testing summarized in Table 2.

Table 2: Non-Clinical Performance Testing

Component	Test Description	Test Result
LINX Device	Mechanical Tensile Strength Test to verify tensile force required to break the device is greater than specification of 3.0 lbs.	Pass
LINX Device	Mechanical Tensile Strength with Suture Knots Test to verify tensile force required to break the sutured knot is greater than 3.0 lbs.	Pass
LINX Device	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
LINX Device	Corrosion Test Cyclic potentiodynamic polarization, in accordance with ASTM F2129-04, on device to determine device susceptibility to corrosion.	Pass (breakdown potentials ≥1276 mV per saturated calomel electrode (SCE))
LINX Device 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. This study was intended for informative purposes only.	The device is nearly fully oxidized with an oxide thickness of approximately 50 Å.
LINX Device	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 were performed per device.	Pass (all 22 devices tested had not failed and could be actuated at the end of the simulated use period)
LINX Device	Magnetic Field Strength Testing* Magnetic field strength vs distance testing for different device configurations. Testing to determine if magnetic field could interfere with a pacemaker or ICD magnetic mode switch. No pre-determined acceptance criteria for this testing were established.	In implant configuration, a 16 bead version of the LINX device did not appear to affect the pacing rate even when placed directly on the surface of a St. Jude Medical pacemaker.
LINX Device	MRI effect on Device** Force applied by 1.5 Tesla coil MRI scan.	Observation only
LINX Device	MRI effect on device** Effect of 1.5 Tesla coil on device magnetic strength.	Observation only
LINX Device	MRI effect on device** Force applied by 3.0 Tesla coil on MRI scan	Observation only
LINX Device	MRI effect on device** Effect of 3.0 Tesla coil on device magnetic strength.	Observation only

* Testing of a single pacemaker (St. Jude Medical Integrity μ SR) to determine the distance required to switch the pacemaker from normal to magnet mode. No testing was conducted to determine whether the LINX device would interfere with sensing electrical signals through the leads which could inhibit or force pacing inappropriately, or unintentionally inhibit or cause a cardioversion (shock). The LINX device is labeled with a precaution "The safety of this device for use in patients with pacemakers and ICDs has not been established."

** There were mixed results at the lower Tesla. The LINX device did not appear to be damaged at 1.5 Tesla; however, the testing results showed that the device is adversely affected at 3.0 Tesla, and may be affected at lower field strengths. The LINX device is labeled as "MR Unsafe."

B. Animal Studies

An animal study was conducted to assess the safety and effectiveness of the LINX™ Reflux Management System. The study was conducted in compliance with Good Laboratory Practice (GLP) per 21 CFR 58 to evaluate the long-term (12 month) performance of the LINX device. A total of 25 Sinclair Mini-Swine had the LINX device placed around the esophagus at the lower esophageal sphincter. The animals were divided into five (5) groups with sacrifice occurring at 42 days (two groups), 91 days, 182 days, and 365 days post device implant. The animals underwent evaluations for:

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.

At sacrifice, all organs appeared normal and all animals had the device 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.

C. Additional Studies

Biocompatibility

The LINX device and the esophagus sizing tool were subjected to biocompatibility testing in accordance with the FDA Guidance "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing'" dated May 1, 1995. The

LINX device is categorized as an implant, permanent (> 30 days) tissue/bone contacting. The esophagus sizing tool is categorized as an implant, limited duration (< 24 hours), tissue/bone contacting. The biocompatibility testing was conducted in compliance with Good Laboratory Practice (GLP) regulations, 21 CFR Part 58. The LINX device (Table 3) and the esophagus sizing tool (Table 4) passed all biocompatibility testing.

Table 3: GLP Biocompatibility Testing for LINX™ device

Test Performed	Test Article	Extract(s)	Test Results
Cytotoxicity ISO 10993-5	Sterilized Implant	E-MEM	Pass
Sensitization ISO 10993-10	Sterilized Implant	0.9% Normal Saline (NS) Polyethylene Glycol (PEG)	Pass
Irritation/ Intracutaneous Reactivity ISO 10993-10	Sterilized Implant	0.9% NS Cotton Seed Oil (CSO)	Pass
Systemic Toxicity: Systemic injection ISO 10993-11	Sterilized Implant	0.9% NS CSO	Pass
Subchronic Toxicity - Subchronic 14-day toxicity ISO 10993-11	Sterilized Implant	0.9% NS	Pass
Genotoxicity: Gene mutation (Ames Assay) ISO 10993-3	Sterilized Implant	0.9% NS PEG	Pass

Table 4: GLP Biocompatibility Testing for the Esophagus Sizing Tool

Test Performed	Test Article	Extract(s)	Test Results
Cytotoxicity ISO0993-5	Sterilized Tool	E-MEM	Pass
Sensitization ISO 10993-10	Sterilized Tool	0.9% Normal Saline (NS) Polyethylene Glycol (PEG)	Pass
Irritation/ Intracutaneous Reactivity ISO 10993-10	Sterilized Tool	0.9% NS Cotton Seed Oil (CSO)	Pass
Systemic Toxicity: Acute Systemic Injection ISO 10993-11	Sterilized Tool	0.9% NS CSO	Pass

Sterilization, Packaging, and Shelf Life

The 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 conducted for the LINX device in accordance with the guidance provided in AAMI/TIR 27, "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 gamma sterilization dose of 25 kGy.

The esophageal sizing tool is a single use device that is supplied non-sterile. The device is to be cleaned and sterilized, by steam autoclave, by the end user. Validations were performed on the esophagus sizing tool to demonstrate the effectiveness of the cleaning and sterilization procedures to be used by the user to meet the AAMI Technical Information Report (TIR) No. 12 "Designing, Testing, and Labeling Reusable Medical Devices for Preprocessing in Health Care Facilities: A Guide for Device Manufacturer." Testing demonstrated an appropriate log reduction of tag spores after cleaning and testing also showed that after exposure to half cycles of common health care facility sterilization procedures, the esophagus sizing tool has a sterility assurance level of 10^{-6}.

After accelerated aging testing designed to simulate four (4) 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 and maintains performance and sterility for a four (4) year shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Clinical data supporting the safety and effectiveness of the LINX device are available from two (2) clinical studies, the feasibility study and the pivotal IDE study. The data obtained from the pivotal study, conducted under IDE G060172, constitutes the main dataset to support the safety and effectiveness of the LINX device, while the data obtained from the feasibility study provide additional supportive data. Data from the pivotal clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Pivotal Clinical Study Design

Patients were treated between January 29, 2009 and September 4, 2009. The database for this PMA reflected data collected through November 22, 2010 and included 100 patients. There were 14 investigational sites (13 U.S. and 1 European). The pivotal clinical study was a prospective, multi-center, single-arm study with subjects serving as their own control. Patients were to be followed for a total of five (5) years. The PMA was submitted after all of the subjects had reached 12 months of follow-up. In addition, 24 month safety and effectiveness data were evaluated on the patients that returned for follow up.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the pivotal study, the "LINX™ Reflux Management System Clinical Study", was limited to subjects who met the following inclusion criteria: were 18-75

years of age, were suitable surgical candidates (i.e., able to undergo general anesthesia and laparoscopic surgery), had documented 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), and required daily proton pump inhibitor or other anti-reflux drug therapy. Subjects also had a total distal ambulatory esophageal pH that was < 4 for $\geq$ 4.5% of time, had symptomatic improvement on PPI therapy demonstrated by a GERD-Health Related Quality of Life (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 and had GERD symptoms in the absence of PPI therapy (minimum 7 days).

Subjects were not permitted to enroll in the pivotal study if they met any of the following exclusion criteria: a history of gastroesophageal surgery, anti-reflux procedures, or gastroesophageal/gastric cancer; any previous endoscopic anti-reflux intervention for GERD and/or previous endoscopic intervention for treatment of Barrett's esophagus; or suspected or confirmed esophageal or gastric cancer. Subjects were excluded if they had any size hiatal hernia > 3 cm as determined by endoscopy, distal esophageal motility (average of sensors 3 and 4) < 35 mmHg peristaltic amplitude on wet swallows or $< 70\%$ (propulsive) peristaltic sequences, and grade C or D esophagitis as determined by the LA Classification system. Other exclusion criteria were a BMI > 35, symptoms of dysphagia more than once per week within the last three (3) months, scleroderma, diagnosed with an esophageal motility disorder (such as, but not limited to, achalasia, nutcracker esophagus, or diffuse esophageal spasm or hypertensive LES), history of or known esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc.), esophageal or gastric varices, Barrett's esophagus, diagnosed psychiatric disorder (e.g., bipolar, schizophrenia, etc.), suspected or known allergies to titanium, stainless steel, nickel or ferrous materials, and those with electrical implants or metallic abdominal implants.

Females who were pregnant, nursing, or planned to become pregnant during the course of the study were also excluded.

2. Follow Up Schedule

All subjects were scheduled to return for follow-up examinations at the times noted in Table 5:

Table 5: 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 (O = optional, X = required)
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

Preoperatively, subjects underwent a health history, GERD-HRQL Questionnaire, Foregut Symptom Questionnaire, recording of PPI, H2, antacid and other medication use, esophageal pH testing, manometry/motility, EGD endoscopy, and barium esophagram (fluoroscopy). Postoperatively, the objective parameters measured during the study included esophageal pH testing at 12 months and symptoms and PPI use at 12 and 24 months (±60 days) from implant date. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

Safety

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

Effectiveness

The primary effectiveness endpoint was assessed by esophageal pH testing at baseline and 12 months. An individual subject was defined as a success if either of the following criteria were met:

- normalization of pH, with normalization defined as pH <4 for no more than 4.5% of monitoring time, OR
- reduction of at least 50% in total time that pH <4, relative to baseline.

Esophageal pH testing was performed with the Bravo pH Monitoring System in all subjects at both baseline and 12 months. The Bravo system involves measuring acid in the esophagus over 24 to 48 hours by using a capsule clipped endoscopically in the distal esophagus.

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)

With regard to success/failure criteria, the study hypothesis for the primary effectiveness endpoint was that the success probability in implanted subjects would be at least 60%. The study success criterion would be met if the lower bound of the one-sided 97.5% confidence interval for the proportion of responders was found to be at least 60%. The hypothesis test was formulated as:

$$\text{Ho: } \pi \leq 0.60 \quad \text{vs.} \quad \text{Ha: } \pi > 0.60,$$

where π is the probability that a subject is classified as a success. The analysis of this hypothesis was carried out using a one-sided exact binomial test.

All subjects were included in the analysis for both safety and effectiveness. For effectiveness, subjects with missing data were considered failures.

There were two (2) secondary endpoints. These included:

1. Reduction in GERD symptoms defined by a validated GERD-HRQL questionnaire. Subject-level success was defined as a reduction of $\geq$ 50% in the total GERD-HRQL score at 12 months post implantation as compared to baseline score off PPI therapy.

   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, which ranged from "no symptoms" to "symptoms are incapacitating." Total scores could range from 0 to a maximum of 50, with larger values indicating more severe GERD.

2. Reduction in PPI use, subject-level success was defined as a reduction in PPI daily use by $\geq$ 50% at 12 months post implantation as compared to a subject's baseline PPI use.

Each of these endpoints would be met if the lower bound of a 97.5% confidence interval for the success rate was at least 60%. The statistical hypothesis for each secondary endpoint was similar to the hypothesis stated above for the primary endpoint. Also, the analyses of the secondary endpoints were based on a one-sided exact binomial test.

B. Accountability of PMA Cohort

At the time of database lock, 100 subjects had been enrolled and treated with the LINX device in the pivotal study, with 90 (90%) subjects available for analysis after two (2) years of follow-up post-implantation.

A total of 103 subjects were found to be eligible and were consented. Of these, 100 subjects were implanted with the device. Three (3) eligible and consented subjects were not implanted, one (1) due to a nickel allergy and two (2) since the enrollment limit for device implantation had been reached. For the purposes of this study, the 100 implanted subjects are considered to form the intention-to-treat (ITT) population.

Figure 6 shows the subject disposition through 12 months.

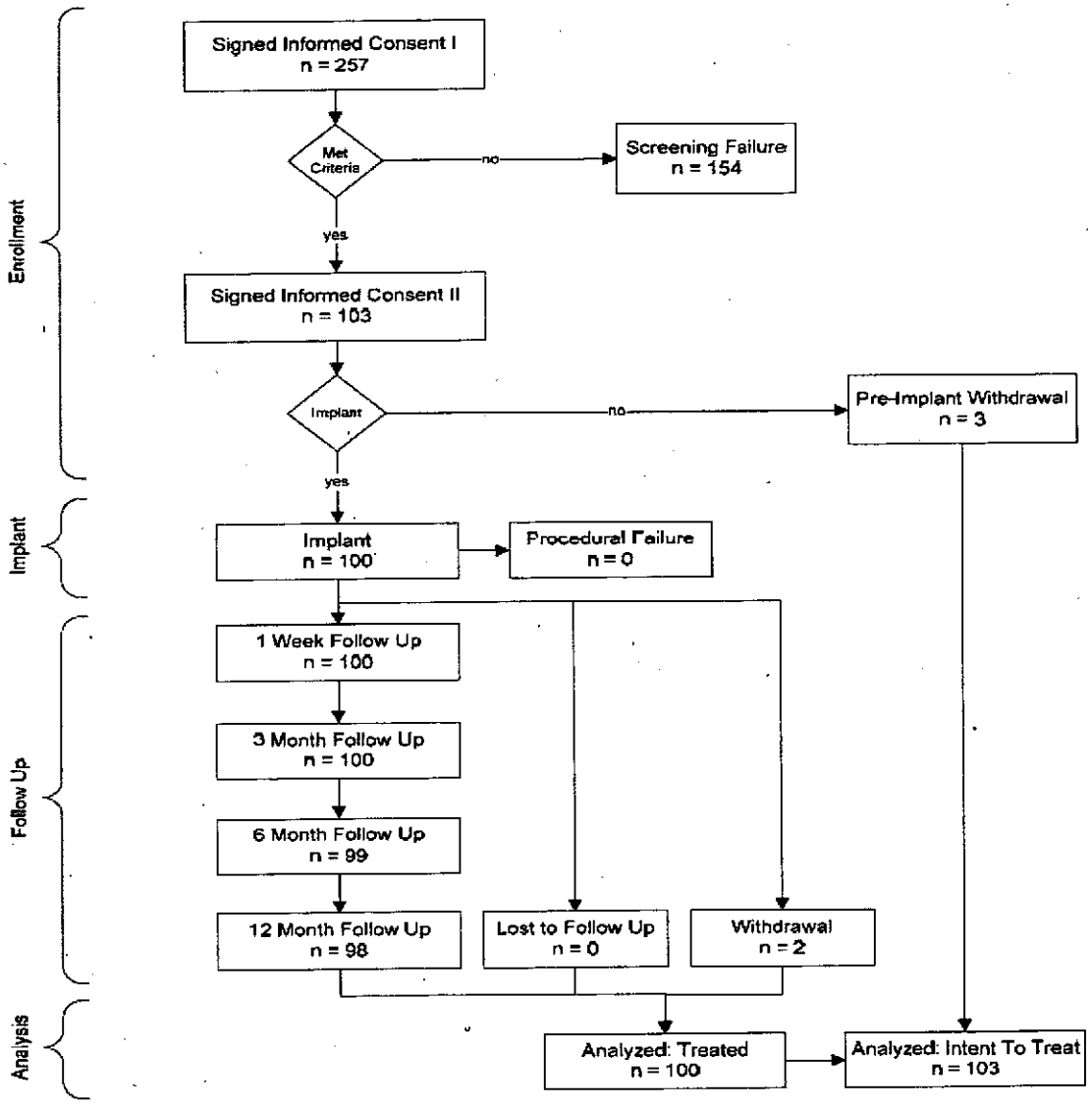


Figure 6: Subject disposition

During the initial 12-month study period, four (4) subjects had their devices explanted and one (1) subject refused to consent for follow-up beyond 12 months. This resulted in a total of 95 implanted subjects who entered the additional 12-month follow-up period. Subsequently, one (1) more subject had the device explanted, and four (4) subjects were lost to follow-up. A total of 90 subjects completed follow-up through 24 months. Table 6 shows an accounting of the subjects through 24 months.

Table 6: Subject accounting at the 24-month follow-up

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)

The original design of the pivotal study called for an assessment of the primary and secondary endpoints at 12 months. The analysis at 12 months included all 100 implanted subjects, regardless of whether they completed the 12-month follow-up visit. Any missing data at 12 months, whether due to loss to follow-up or device explants, was imputed as a failure. The length of follow-up was later increased to 24 months post-implant; however, the applicant did not collect any information on the primary endpoint after the month 12 follow-up visit. Thus, the applicant's analysis of effectiveness at 24 months was based solely on the two (2) secondary endpoints. Furthermore, the month 24 analysis was based only on the 90 subjects who had their 24-month follow-up evaluation. This analysis is overly optimistic since it does not account for the subjects who had a device explant or were lost to follow-up. FDA conducted an ITT analysis in which all 100 implanted subjects were included in the 24 month analysis.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population were felt to be typical for a study performed in the U.S. Demographics and baseline values are summarized briefly in Table 7.

Table 7: Baseline Demographics

Characteristic	N	Mean ± SD (Median)	Range
Age (years)	100	50.4±12.4 (53.0)	18.3, 74.7
Body Mass Index (BMI)	100	27.9±3.4 (27.9)	19.8, 34.7
Characteristic	**% (n/N)**		
Gender			
Male	52.0% (52/100)		
Female	48.0% (48/100)		
Race			
Caucasian/Non-Hispanic	96.0% (96/100)		
Black	0.0% (0/100)		
Hispanic	3.0% (3/100)		
Other	1.0% (1/100)		
BMI Class			
Normal (<25)	19.0% (19/100)		
Overweight (≥25 and <30)	55.0% (55/100)		
Obese (≥30)	26.0% (26/100)		

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The following items further characterized the study subjects at baseline:

- Mean duration of GERD was 12.8 years
- Mean duration of PPI use was 6.3 years
- Mean GERD-HRQL score off PPI therapy was 26.6 and on PPI therapy was 12.0
- 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

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on ITT cohort of 100 evaluable subjects available for the 24 month evaluation. The key safety outcomes for this study are presented below in Tables 8 to 10.

There were no cases of esophageal erosion or device migration as assessed by upper endoscopy and chest x-rays in any of the subjects that were evaluated up to the 24-month time point. At 12 months, 93 of the 96 subjects evaluated with a barium esophagram had normal swallow function; there were three (3) subjects with abnormal function, one (1) of whom required dilation.

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, as seen in the Table 8. The majority of adverse events resolved without sequelae.

Table 8: 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)
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%
Decreased Appetite	4	4% (4)	4	4% (4)	0	0%	0	0%

	Related or Unknown		Mild		Moderate		Severe	
Adverse Event	AEs (n)	Subj. % (n)	AEs (n)	Subj. % (n)	AEs (n)	Subj. % (n)	AEs (n)	Subj. % (n)
Belching	2	2% (2)	2	2% (2)	0	0%	0	0%
Flatulence	2	2% (2)	2	2% (2)	0	0%	0	0%
Weight Loss	2	2% (2)	2	2% (2)	0	0%	0	0%
Food Impaction	1	1% (1)	0	0%	1	1% (1)	0	0%
Globus Sensation	1	1% (1)	1	1% (1)	0	0%	0	0%
IBS/Dyspepsia	1	1% (1)	1	1% (1)	0	0%	0	0%
Regurgitation of Sticky Mucus	1	1% (1)	0	0%	1	1% (1)	0	0%
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 the throat. Twelve (12) of these subjects had at least two (2) dilations and 10 of these subjects continued to have symptoms. The second most common event experienced by subjects was pain (25 events in 24 subjects).

There were nine (9) serious device- or procedure-related adverse events reported in six (6) subjects (6%), as seen in the Table 9.

Table 9: 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	1% (1)
Vomiting	2	1% (1)
Odynophagia	1	1% (1)
Pain[1]	1	1% (1)

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

Regarding the time to onset, there were 149 device- or procedure-related adverse events that occurred between 0 and 180 days. There were also 13 events considered related to the device/procedure or of unknown relationship that occurred after 180 days; one (1) of these events was considered serious. This subject experienced chest pain, nausea, and symptoms of indigestion (day 235 post implant). This is shown in Table 10.

Table 10: 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)

There were five (5) subjects who had the device explanted. Three (3) subjects had the device explanted for dysphagia, with two (2) of these subjects then electing to have a Nissen fundoplication. Details of the five (5) explants are given below:

- One (1) subject with history of severe heartburn, severe regurgitation, and frequent and prolonged nausea, experienced nausea coupled with dysphagia within two (2) weeks of device implantation. The subject underwent balloon dilation in the region of the gastroesophageal junction (GEJ) without resolution of symptoms and the subject requested to have the device removed at 30 days post-implant.

- One (1) subject with history of GERD started with dysphagia within five (5) days of device implantation. The subject underwent esophageal dilation without resolution of symptoms. Subsequent manometry/motility testing was performed and showed loss of esophageal motility. The device was removed on post-operative day 21.

- One (1) subject started with dysphagia within five (5) days post-implant and odynophagia within seven (7) days post-implant. Esophageal dilations of the GEJ were performed without resolution of symptoms and the device was removed 93 days post-implant.

- One (1) subject started with intermittent vomiting within three (3) months of device implantation. The subject was subsequently diagnosed with a Helicobacter pylori infection and started on medication. The symptoms continued and the device was explanted at 357 days post-implant.

- One (1) subject with recurrent GERD symptoms elected to have the device removed so a Nissen fundoplication could be performed. This occurred 489 days post-implant.

2. Effectiveness Results

The study did not meet the primary effectiveness endpoint, although the secondary endpoints were met. The analysis of effectiveness was based on 100 evaluable subjects at the 12-month time point. The key effectiveness outcome is presented in Table 11. Note that the secondary endpoints were assessed at both 12 and 24 months.

Primary Endpoint
As discussed previously, 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 ≤ 4.5% of monitoring time, or
- there was a reduction of at least 50% in total time that pH <4, relative to baseline.

This endpoint would be met if the lower bound of a 97.5% confidence interval for the success rate was at least 60%.

Table 11 summarizes the analysis for the primary effectiveness endpoint (pH testing). Sixty-four (64) of the 100 implanted subjects achieved success (either pH normalization or a ≥50% reduction in distal esophageal acid exposure), and the lower limit of the 97.5% confidence interval was 53.8%. Since, this lower bound fell below the 60% success threshold, the primary endpoint was not met.

Table 11: 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%

Of the 64 subjects who were successful on the primary endpoint, 56 subjects had pH normalization and eight (8) subjects had at least 50% reduction in total time that pH <4, relative to baseline. For the eight (8) subjects who met the primary endpoint by having at least a 50% reduction in total time that pH <4, the majority had improved GERD symptoms and reduction in PPI usage.

Secondary Endpoints
The first secondary endpoint was reduction in GERD symptoms defined by the GERD-HRQL questionnaire. 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. Table 12 shows the percentage of subjects successful in meeting this endpoint at 12 and 24 months for the total number of subjects in the study (i.e., ITT group). If only the subjects who returned for follow up and evaluation at 24 months were analyzed, 93.3% (84/90) of subjects met the endpoint; however, this analysis using only the 90 subjects who completed follow up through 24 months is too optimistic since it ignores the subjects who were explanted or lost to follow up.

Table 12: Summary of success rate for reduction in GERD-HRQL scores

Follow-up time	Success rate	95% CI
Month 12	92% (92/100)	(85%, 96%)
Month 24	84% (84/100)	(75%, 91%)
Month 24	93% (84/90)	(86%, 98%)

As seen above, the majority of subjects had at least 50% improvement in their scores. Overall, the post-baseline scores were fairly consistent across the study duration to 24 months.

The second secondary endpoint was reduction in PPI use. 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. Table 13 shows the percentage of subjects successful in meeting this endpoint at 12 and 24 months for the total number of subjects in the study (i.e., ITT group). At 24 months, if only the subjects who returned for follow-up and evaluation were examined, 96% (86/90) of subjects met the endpoint. In addition, at 12 months 91% of evaluable subjects eliminated their daily PPI use and, at 24 months, 92% of evaluable subjects eliminated their PPI use.

Table 13: Summary of success rate for reduction in PPI usage

Parameter	Follow-up Time	Success Rate	95% CI
≥50% reduction in daily PPI use (secondary endpoint)	12 months	93% (93/100)	86%, 97%
	24 months (treatment group)	86% (86/100)	78%, 92%
	24 Months (evaluable subjects)	96% (86/90)	89%, 98%
Elimination of daily PPI use	12 months (evaluable subjects)	91% (88/97)	83%, 96%
	24 Months (evaluable subjects)	92% (83/90)	85%, 97%

Additional Data

In obtaining the primary endpoint of pH testing, other components of the DeMeester Score, as well as the composite score were also able to be examined. It is the composite score, which is made up of these individual components pertaining to acid exposure time, frequency, and duration, that has been reported to be the most reliable measurement of a therapeutic acid suppression regimen or an effective antireflux operation, with sensitivity and specificity for GERD at 96%.[1] As such, it is important to note that even though there was improvement in the composite DeMeester score in 52% of subjects that had pH testing at 12 months, the percentage of subjects that have this improvement is lower than the percentage of subjects that met the primary effectiveness endpoint. This is seen in the Table 14.

Table 14: pH Parameters of Esophageal Acid Exposure

DeMeester Components	Normal Values	Baseline	12 Months
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
# of Episodes pH <4	36.8	175.0±81.7 (161.0) N=100	82.8 ± 67.6 (67.0) N=96
# of Episodes > 5 min	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	<14.72	41 .0±16.3 (36.6) N=97	18.7 ± 17.3 (13.5) N=95
Percentage of subjects with normal DeMeester score		0%	52% (49/95)

Foregut Questionnaire

Additional GERD-related symptoms were assessed by the Foregut Questionnaire, which is not a validated instrument. Of note is that there was improvement in severity and frequency of regurgitation and heartburn over the course of the study.

For difficulty swallowing, the percentage of subjects reporting dysphagia increased as the study progressed (from 23% reporting dysphagia at baseline to 45.6% reporting dysphagia at 24 months). There was also an increase in the number of subjects who reported needing liquids for clearing (from 4% to 7.4% to 12.2%) as the study progressed.

Table 15: Side Effects and Additional Clinical Outcomes

	Baseline[1]	12 Months[1]	24 Months[1]
Inability to Belch	0%	1%	0%
Inability to Vomit	0%	0%	1%
Bloating Frequency – Frequently/Continuously	40%	5%	7%
Heartburn – Severe or Moderate	89%	3%	6%
Heartburn – Mean frequency/week	79	2	2
Regurgitation – Severe or Moderate	57%	2%	1%
Regurgitation – Mean frequency/week	28	1%	1%
Absence of Extra-Esophageal Symptoms	49%	86%	88%
Chest Pain	69%	20%	16%
Difficulty Swallowing	23%	44%	46%
Difficulty Swallowing – requiring liquids for clearing	4%	7%	12%
Difficulty Swallowing – Mean frequency/week	1	2	1
Patient Satisfied with Present Condition Off PPI On PPI	 0% 13.0%	 957% NA	 90% NA

[1]Assessments completed off PPI therapy, unless noted

Esophagitis

The status of esophagitis was examined at 12 and 24 months. Subjects with esophagitis of Grade C or D (LA Classification) at baseline were excluded from participation in the study. No subject developed Grade C esophagitis during the course of the study. At both 12 and 24 months the majority of subjects had improvement or no change in their esophagitis status.

As shown in Table 16, at 12 months, subjects who improved their esophagitis scores or remained stable are shown in green, while subjects who had worsening in their esophagitis are shown in red. Of the 60 subjects with no esophagitis at baseline, 56 continued to have no esophagitis and for the remaining four (4) subjects, three (3) developed Grade A esophagitis and no information was available for one (1) subject. Twenty two (22) subjects had Grade A esophagitis at baseline, 16 improved to no esophagitis, and the remaining six (6) subjects either continued to have grade A esophagitis, progressed to Grades B or D esophagitis, or no information was available. There were 18 subjects with Grade B esophagitis at baseline, all subjects improved; 13 subjects had no esophagitis and the five (5) subjects to Grade A.

Table 16: Esophagitis at Baseline and 12 Months

	Month 12					
Baseline	None	Grade A	Grade B	Grade D	NA	Total
None	56	3		0	1	60
Grade A	16	2	1	1	2	22
Grade B	13	5	0		0	18
Total	85	10	1	1	3	100

Table 17 shows similar outcome for subjects with esophagitis at 24 months as compared to baseline. Of the 60 subjects with no esophagitis at baseline, 49 had no esophagitis, four (4) subjects developed Grade A and there was no information available for seven (7) subjects. Of the 22 subjects with Grade A esophagitis at baseline, 15 improved to no esophagitis and the remaining seven (7) subjects either continued to have Grade A esophagitis, progressed to Grade B esophagitis or no information was available. For the 18 subjects with Grade B esophagitis at baseline, most showed improvement to no esophagitis (15 subjects) or Grade A esophagitis (1 subject), one (1) subject continued to have Grade B esophagitis.

Table 17: Esophagitis at Baseline and 24 Months

	Month 24				
Baseline	None	Grade A	Grade B	NA	Total
None	49				60
Grade A	15	2			22
Grade B	15	1	1		18
Total	79	7	3	11	100

Manometry

Manometry was performed at baseline and 12 months. At 12 months, 31 out of the 32 subjects who had a hypotensive LES at baseline were evaluated and three (3) remained hypotensive. Fifteen (15) of 93 subjects had <70% effective swallows and four (4) had distal esophageal amplitude <35 mmHg. One (1) subject was reported to have ongoing complaints of dysphagia and abnormal motility. No other significant differences were seen in measures between baseline and 12 months.

Conclusions drawn from the study

Safety Conclusions

The safety of the LINX Reflux Management System in the treatment of subjects with GERD was based on adverse event data from 100 subjects followed for up to 24 months. The 12 month data demonstrated 162 total adverse events reported in 76% of the subjects. Most adverse events resolved without sequelae. Dysphagia was the most common adverse event with 76 events being reported in 68% of the subjects, with 11% of the subjects reporting ongoing dysphagia. Eighteen (18) subjects underwent esophageal dilatation and 10 continued to have dysphagia at 24 months. Furthermore, there were several subjects who experienced symptoms of odynophagia/dysphagia that started after 180 days (182-605) and several subjects who had odynophagia and/or dysphagia that took over 180 days to resolve (maximum time noted 447 days). Overall, the incidence of dysphagia was found to be comparable to the incidence of dysphagia that is reported in patients undergoing anti-reflux surgery, such as Nissen fundoplication.[2] Overall, the safety data from the pivotal trial supports a reasonable assurance that the LINX device is safe.

Effectiveness Conclusions

While the success criterion for the pre-specified primary objective of the study (pH normalization or a $\geq$ 50% reduction in distal esophageal acid exposure) was not met, there was improvement in esophageal pH. Sixty four (64) of 100 subjects met the primary endpoint; there were 56 subjects who had normalization of pH and another eight (8) subjects who had a least a 50% reduction in total time that the pH < 4, however the lower limit of the 97.5% confidence interval was only 53.8% instead of the pre-specified 60%.

Even more subjects had success in meeting the secondary objectives of improvement in GERD symptoms and reduction in PPI usage. The success rate for reduction in GERD symptoms was 92% at 12 months and 84% at 24 months. Similarly, reduction of at least 50% in PPI use was seen in 93% of subjects at 12 months and 86% at 24 months. The majority of these subjects, 88 at 12 months and 83 at 24 months, eliminated their use of PPIs.

Although the primary objective of the study was not met, FDA considered the improvement in esophageal pH that was seen in 64% of subjects in addition to the improvement in GERD symptoms and reduction in PPI medication use demonstrated a reasonable assurance as to the effectiveness of the LINX Reflux Management System.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Feasibility Study

Clinical data supporting the safety of the LINX Reflux Management System are also available from a Feasibility study. This study was performed to collect safety information, performance data, and develop procedural optimization for the LINX device in the treatment of GERD. The results are summarized below.

Study Design

The feasibility study was a prospective, multi-center, single-arm study with subjects serving as their own control. The device was implanted in 44 subjects at four (4) sites (two (2) U.S. and two (2) European).

Objectives

The primary performance objectives were to monitor improvements in the subject's GERD symptoms by using the GERD-HRQL and reduction in PPI use. In addition, pH monitoring was used as an objective, physiological measurement to demonstrate improved LES function through pH score improvement (normalization) or $\geq$ 50% improvement. There were no statistical hypotheses for this study.

The specific objectives were the following:

Clinical endpoint: safety

To evaluate the incidence of all adverse events up to 60 months post implant.

Clinical Endpoint: effectiveness

To monitor the improvement of GERD symptoms, PPI use, and esophageal acid reduction at various time points up to 60 months post implant and optimize the implant technique.

Demographics and baseline parameters

At baseline, 59% of the subjects were male, 41% were female, and the mean age was 42.8 years. Mean BMI was 25.7, mean amount of time pH <4 was 11.9%, and mean GERD-HRQL score was 26.6.

Safety results

There were no cases of esophageal erosion or device migration as assessed by upper endoscopy and chest x-rays in any of the subjects that were evaluated up to the 36 month time point. The majority of subjects evaluated with barium esophagram had normal swallow function and esophageal peristalsis.

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 (3) months, two (2) subjects required dilation in the area of the gastroesophageal junction (GEJ) and one (1) subject had the device removed. Other common adverse events included pain, nausea, and vomiting. No intra-operative

complications, deaths, life-threatening events, device erosions, device migrations, or infections were reported.

Two (2) subjects had serious adverse events related to the device and procedure that included one (1) device removal for dysphagia and one (1) hospitalization for chest pain <30 days following the device implant procedure. Both events resolved without clinical sequelae.

There were three (3) subjects who had the device explanted. Reasons for explant included ongoing dysphagia, elective removal due to recurrent heartburn, and need for an MRI study.

- One (1) subject had persistent dysphagia treated by device removal at 226 days post-implant without incident. The dysphagia resolved and the subject went on to have a Nissen fundoplication at a later time (this is one of the serious adverse event reported above).

- One (1) subject experienced neurological and vascular symptoms unrelated to the device and procedure. The study subject requested removal of the device in order to undergo this MRI procedure. The Investigator complied with this request and removed the device 468 post-implant without incident.

- One (1) subject continued to experience recurrent heartburn. A decision was made to remove the device and perform a Nissen fundoplication. The device was removed 1302 days post-implant without incident.

Effectiveness results

For the subjects who returned for evaluation and follow-up, improvement in GERD-HRQL scores by ≥50% occurred in 97.4% (38/39) at 12 months, 88.6% (31/35) at 24 months, and 96.3% (26/27) at 36-months.

For the subjects who returned for evaluation and follow-up, the percentage of subjects off PPI therapy completely or having reduced their PPI therapy by ≥ 50% was 89.7% (35/39) at 12 months, 82.9% (29/35) at 24 months, and 87.5% (28/32) at 36 months.

For the subjects who returned for evaluation and follow-up, the percentage of subjects with pH normalization or a ≥50% reduction in distal acid exposure was 79.5% (31/39) at 12 months, 90% (18/20) at 24 months, and 85% (17/20) at 36 months. Esophageal pH monitoring is not performed in any of the US subjects beyond the 12-month follow-up time point.

Conclusions drawn from the feasibility study

The safety and effectiveness results are similar to those observed in the Pivotal IDE study. Dysphagia was the most common adverse event. The majority of subjects demonstrated improvement in GERD symptoms and pH, and reduction in PPI use.

European Experience

The LINX Reflux Management System is currently marketed in Italy, Germany, and England. As of November 2011, there had been 98 implants in these countries. Feedback from the implanting centers suggest that the effectiveness of the LINX device is consistent with what has been shown in clinical trials. A few adverse events have been reported. One (1) subject had complaints of odynophagia following the LINX procedure and had the device removed with fundoplication performed. This occurred approximately seven (7) months following the implant and the odynophagia was reported to have resolved without sequelae. One (1) subject had dysphagia and underwent dilation with reported resolution of symptoms. Another patient had cardiac arrest following laparoscopic surgery to implant the LINX device. Although the event was considered not related to the LINX device or procedure, a Field Experience Report was submitted. Torax Medical has implemented a European Registry to track outcomes following the LINX procedure. As of July 2011, 23 subjects had been enrolled in the registry and no data is yet available beyond the implant procedure.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on January 11, 2012, the Gastroenterology and Urology Devices Panel voted 9-0 that there is reasonable assurance the device is safe, effective, and that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. The meeting transcript may be accessed at the following webpage:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeeting Materials/MedicalDevices/MedicalDevicesAdvisoryCommitte/Gastroenterology-UrologyDevicesPanel/UCM291391.pdf

B. FDA's Post-Panel Action

The panel recommended that the sponsor conduct two (2) Post Approval Studies to evaluate the long-term safety and effectiveness of the LINX device in the treatment of Gastroesophageal Reflux Disease. Torax Medical Inc. will continue follow-up on the 100 patients enrolled in the IDE study for five (5) years post implantation. They will also evaluate an additional 200 patients implanted with the LINX Reflux Management System enrolled in a new clinical study for five (5) years post implantation. The panel recommendations have been incorporated in to the proposed design of the post-approval studies.

Even though the clinical study excluded patients with Barrett's esophagus, Grade C or D esophagitis, and motility disorders, the panel recommended that the use of the LINX device in patients with these conditions not be restricted, instead, patients and physicians are warned that the safety and effectiveness of the LINX device has not been evaluated in patients with Barrett's esophagus, Grade C or D (LA classification) esophagitis, or major motility disorders. These recommendations were incorporated into the final labeling.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The safety of the LINX Reflux Management System in the treatment of subjects with GERD was based on adverse event data from 100 subjects followed for up to 24 months. The 12-month data demonstrated 162 total adverse events reported in 76% of the subjects. Dysphagia was the most common adverse event with 76 events being reported in 68% of the subjects. There were a total of nine (9) serious adverse events related to the procedure and or device. There were no device erosions, migrations, or deaths seen in the study.

B. Effectiveness Conclusions

Although the study did not meet its primary effectiveness endpoint (of at least 60% of subjects achieving either normalization of esophageal pH or a reduction of at least 50% in total time that pH is less than 4 relative to baseline), when all the data from the study are evaluated, including symptom improvement and reduction in GERD medication use, there is an overall benefit of the LINX device for the treatment of GERD. At 12 months, 92% of subjects had at least a 50% improvement in their symptoms as measured by the GERD-HRQL and 93% of subjects had at least a 50% reduction in PPI use.

C. Overall Conclusions

Torax Medical Inc. has provided valid scientific data that supports the reasonable assurance of safety and effectiveness of the LINX™ Reflux Management System when used in accordance with the indications for use - in patients diagnosed with Gastroesophageal Reflux Disease (GERD) as defined by abnormal pH testing and who continue to have chronic GERD symptoms despite maximum medical therapy for the treatment of reflux.

There is an unmet need for patients who suffer from symptoms of gastroesophageal reflux disease who are not fully responsive to medication use but who may not wish to pursue Nissen fundoplication surgery. The benefits of treatment with the LINX device, including improvement in GERD symptoms, reduction or elimination of medication, and improvement in esophageal pH, outweigh the risks associated with the use of the device. Although the primary endpoint of the clinical study was not met, the FDA Advisory Panel and the FDA agree that the preponderance of the data support the use of the LINX Reflux Management System in patients who met the criteria specified in the proposed indication for use. Torax Medical will continue to evaluate the safety and effectiveness of the LINX device in two (2) Post Approval Studies.

XIV. CDRH DECISION

CDRH issued an approval order on March 22, 2012. The final conditions of approval cited in the approval order include an agreement to conduct two (2) post-approval studies that will evaluate the long-term effectiveness of the device and the incidence of adverse events. The first study will continue to follow patients enrolled in the IDE pivotal study. The second study will enroll new patients in at least 20 to 25 study centers throughout the US.

1. **Extended 5-year follow-up of the PMA cohort:** This will be a prospective, multicenter, single arm clinical study that will be conducted in the United States and Europe. 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).

   The study will continue to follow the 90 patients available in the IDE pivotal study, for five (5) years post-implant. Follow-up in-office assessments will occur at 36, 48, and 60 months. The rate of occurrence for serious device and procedure related adverse events will be estimated. A follow-up rate of at least 80% will have to be maintained. The study will also assess continued effectiveness by comparing GERD-HRQL scores at baseline vs. at 60 months post implantation.

2. **5-year New Enrolment Study:** This will be a prospective, multicenter, single-arm observational study performed in 20 to 25 centers in the United States. The purpose of this study is to monitor the safety and effectiveness of the LINX implant procedure and device in a post-approval environment to supplement existing safety and effectiveness data. A minimum of 200 patients will be enrolled in the study. The study centers will include pivotal centers and at least 10 centers with no prior LINX experience. All patients will be evaluated in-office at baseline, 12 months, and then annually for five (5) years post implant. The study will monitor safety endpoints including serious adverse events. The primary effectiveness endpoint will be that at least 60% of subjects will have a 50% reduction in total GERD-HRL score, as indicated by the lower bound of a 97.5% confidence interval (based upon a one-tailed test). The esophageal pH endpoint will be evaluated in all 200 patients annually, as well as the percent mean reduction in total percent time of pH less than four (4), percent of study patients with normalization or at least a 50% reduction from baseline in total percent time of pH less than four (4), and a summary of the DeMeester components of total DeMeester score.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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

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