Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee

LINX™ Reflux Management System

January 11, 2012

Torax Medical, Inc.
CONFIDENTIAL
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Executive Summary

The LINX™ Reflux Management System, developed and manufactured by Torax Medical of St. Paul, MN, is currently under review by the U.S. Food and Drug Administration (FDA) for the following indication:

The 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.

The primary medical therapy for GERD is the daily use of proton pump inhibitors (PPIs). PPI therapy is highly effective in healing esophagitis, but less effective in controlling reflux-related symptoms. Multiple studies have shown symptom control failure rates of up to 40% in patients with non-erosive GERD. PPI therapy does not address the barrier defect and is therefore often ineffectual in preventing severe regurgitation and non-acid reflux symptoms. Many of the patients with incomplete response to medical therapy are reluctant to having antireflux surgery. Surgical fundoplication, although effective in restoring a barrier, permanently alters the gastric anatomy and is associated with undesirable side effects. Further, it is a surgical procedure that is complex and difficult to standardize. Today, most referrals for a surgical fundoplication are typically reserved for patients with large hiatal hernias or advanced reflux disease, such as Barrett’s esophagus. At present, there are no intermediary treatment options for the patient who falls in the gap between PPIs and fundoplication surgery. Patients in this “Therapy Gap” are in a predicament: either accept life-long PPI therapy with insufficient symptom relief or commit to a fundoplication with its attendant side effects. Alternative GERD treatments are needed which can correct the barrier defect in a more comprehensive and less invasive manner with freedom from undo side effects. The LINX System is intended to address this unmet need for patients caught in the GERD therapy gap.
The pathogenesis of GERD is multifactorial, but of primary importance is the gastroesophageal barrier that prevents the reflux of gastric juice into the esophagus. The barrier, termed the lower esophageal sphincter (LES), provides a high pressure zone between the esophagus and stomach. The effectiveness of the LES as a barrier is dependent on its ability to resist opening in response to challenges from gastric distention. Based on this premise, the LINX System was designed to improve the barrier’s function by using forces of magnetic attraction. Precise forces are created by special magnets being attracted to each which help the sphincter resist opening when challenged by increases in gastric pressures which result in reflux. The LINX device is a miniature expansible band of connected titanium beads, each containing a magnetic core. The device is placed laparoscopically around the gastroesophageal junction (GEJ) using standard laparoscopic tools and technique. The totality of the magnetic attraction between adjacent beads augments the ineffective esophageal sphincter (Figure 1-ES). On swallowing food or liquids the esophageal peristaltic wave creates a pressure in the esophageal body which is sufficient enough to overcome the magnetic bond between beads. This significantly reduces the force of attraction between beads and allows the device to expand and accommodate the swallowed bolus (Figure 2-ES). Importantly, when closed, the LINX device does not compress the esophageal wall closed. It simply helps the sphincter from opening to challenges of gastric pressures (Figure 3-ES).
The LINX Reflux Management System has been evaluated in two FDA approved IDE trials. The complete IDE cohort includes 144 subjects with follow-up data between two and four years. The results of these trials show real-world clinical success, and provide reasonable assurance of safety, and efficacy. In 144 laparoscopic surgeries for LINX implantation, there have been no unanticipated adverse device events (UADEs). A serious adverse event (SAE) related to the device or implantation procedure has occurred in 6% (8/144) of subjects. Importantly, no subjects have been permanently harmed or disabled by the LINX device or procedure. There have been no reports of device erosion, migration or infection. If necessary the LINX device can be safely removed by a laparoscopic procedure.

The Feasibility IDE study enrolled 44 subjects at four clinical sites (2 US and 2 OUS). The benefits of esophageal acid reduction, symptom improvement, and elimination of PPI dependence have been reported out to 3 years. Based on the clinical results of the Feasibility trial the LINX device received CE Mark approval in September 2008. At the present time the LINX device is marketed in the United Kingdom, Germany and Italy.

The Pivotal IDE study represents the most recent body of clinical evidence for the LINX System. A total of 100 subjects, at 14 clinical sites (13 US and 1 OUS), were implanted with the LINX device. The Pivotal trial was well executed by established thought leaders at both academic and community-based hospitals. In the Pivotal study design the study subjects served as their own control. This decision was prompted by the fact that the study subjects were from the therapy gap and lacked established effective treatment options for a comparative control group. Indeed patients who have an established insufficient response to PPI therapy have already exhausted this treatment option and decline to have a surgical fundoplication due to concern over side-effects. The trial endpoints were assessed at 12 months following the implant procedure. The subjects continue to be followed, and the study population has now completed follow-up at 24 months. Follow-up compliance was exceptional; 100% at 12 months and 95% at 24 months.
The Pivotal trial study subjects had a long-standing history of GERD with a mean duration of 6.3 years of PPI use. All 100 subjects were implanted with the LINX device with a mean duration of the implantation procedure of 39 minutes. Fifty percent of the study subjects were discharged from the hospital on the same day as the surgery on an unrestricted diet and the others the day after surgery. No intra-operative or hospital complications occurred that prolonged hospitalization.

The primary safety endpoint measured the rate of related device and procedure serious adverse events (SAEs). The efficacy endpoints were assessed off PPI therapy and measured esophageal acid exposure, total GERD-HRQL scores (a validated questionnaire for quality of life with GERD), and PPI usage. A summary of the study endpoints is presented below (Table 1-ES).

The related SAE rate was 6% (9 events in 6 subjects), less than the estimated SAE rated of 10%. Three subjects underwent device removal for dysphagia and/or odynophagia prior to the 3 month follow-up without complications or clinical sequelae. The dysphagia and odynophagia resolved in all cases following explant of the device. Two subjects were re-hospitalized <7 days after the implant procedure for nausea and/or vomiting. The sixth subject was hospitalized for chest pain about 6 months after the implant; and later at about 12 months, the device was removed for vomiting of unknown etiology, but for which gastroparesis was ruled out.

The primary efficacy of pH normalization or a >50% reduction was met by 64% of the subjects. This produced a 95% confidence interval (CI) range of 54% to 73%. This slightly missed the lower bound efficacy threshold of 60% but still shows most subjects achieved this clinical benefit. Esophageal acid exposure data for the study population did show the mean total acid exposure (percent time pH<4) was reduced by more than half, from 11.9% at baseline to 5.4% at 12 month post LINX implantation. Both efficacy secondary endpoints substantially exceeded the required success criteria; 92% of subjects met the endpoint of improvement in GERD-HRQL symptom score, and 93% met the endpoint of reduced PPI use. Improvement in GERD symptoms and reduction in PPI use was not dependent upon meeting the primary endpoint; that is, even subjects who did not experience a 50% or greater
reduction in pH showed large reduction in symptoms (mean GERD-HRQL total score decreased from 28.4 at baseline to 5.9 and 5.5 at 12 and 24 months) and absence in daily PPI use (79% and 83% free from daily dependence compared with 0% at baseline). As shown in Table 2-ES, subjects who did not achieve primary endpoint success criteria continue to enjoy significant clinical benefits at two years.

### Table 1-ES: Summary of Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Study Objective</th>
<th>Treatment Group N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Safety</strong></td>
<td>Estimate the rate of serious device and procedure related adverse events with a sufficient level of precision.</td>
<td>SAE reported in 6 subjects. SAE rate = 6.0%</td>
</tr>
<tr>
<td><strong>Primary Efficacy</strong></td>
<td>≥60% of subjects will have normalized or improved by ≥50% in total time acid exposure of pH &lt;4, as indicated by the lower bound of a 97.5% confidence interval.</td>
<td>64% of subjects normalized or improved total time by ≥50%. The lower 97.5% confidence limit was 54% (p = 0.24).</td>
</tr>
<tr>
<td><strong>Secondary Efficacy #1</strong></td>
<td>≥60% of subjects will have ≥50% reduction in total GERD-HRQL scores, as indicated by the lower bound of a 97.5% confidence interval.</td>
<td>92% of subjects had ≥50% reduction in total GERD-HRQL scores (lower confidence limit = 85%)</td>
</tr>
<tr>
<td><strong>Secondary Efficacy #2</strong></td>
<td>≥60% of subjects will reduce their average daily PPI dosage by ≥50%, as indicated by the lower bound of a 97.5% confidence interval.</td>
<td>93% of subjects had ≥50% reduction in their average daily PPI dosage (lower confidence limit = 86%)</td>
</tr>
</tbody>
</table>

### Table 2-ES: Clinical Benefit in Subjects Missing the Primary Efficacy Endpoint (n=36)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Months1</th>
<th>24 Months1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of Daily PPI Use</td>
<td>0%</td>
<td>78.8%</td>
<td>82.7%</td>
</tr>
<tr>
<td>Mean Total GERD-HRQL2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off PPI</td>
<td>28.4</td>
<td>5.9</td>
<td>5.5</td>
</tr>
<tr>
<td>On PPI</td>
<td>14.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Regurgitation - Severe or Moderate</td>
<td>72.2%</td>
<td>6.3%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>44.4%</td>
<td>21.1%</td>
<td>17.2%</td>
</tr>
<tr>
<td>Patient Satisfied with Present Condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off PPI</td>
<td>0%</td>
<td>96.9%</td>
<td>86.2%</td>
</tr>
<tr>
<td>On PPI</td>
<td>5.6%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

1 Assessments completed off PPI therapy.
2 Lower GERD-HRQL scores correspond to an improvement.
Additional measures of clinical effectiveness defined in the protocol, in addition to the trial endpoints, also showed significant clinical benefit. These benefits included an excellent side effect profile for an anti-reflux surgical procedure (preserving the physiologic function to belch or vomit, and not increasing stomach bloat), reduction in severity and frequency of regurgitation, improvement in esophagitis, improvement in extra-esophageal symptoms, and greater patient satisfaction with present condition than at baseline. A summary of this information is detailed below (Table 3-ES).

Table 3-ES: Additional Measures of Clinical Effectiveness – All subjects

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>12 Months(^1)</th>
<th>24 Months(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to Belch</td>
<td>0%</td>
<td>1.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Inability to Vomit</td>
<td>0%</td>
<td>0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Bloating Frequency – Frequently/Continuously</td>
<td>40.0%</td>
<td>5.3%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Regurgitation – Severe or Moderate</td>
<td>57.0%</td>
<td>2.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Regurgitation – Mean frequency/week</td>
<td>27.9</td>
<td>1.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>40.0%</td>
<td>12.3%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Absence of Extra-Esophageal Symptoms</td>
<td>49.0%</td>
<td>86.3%</td>
<td>87.8%</td>
</tr>
<tr>
<td>Patient Satisfied with Present Condition</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Assessments completed off PPI therapy

Results from both the Feasibility and Pivotal trials provide clear evidence that the benefits obtained with the LINX Reflux Management System outweigh its risks. The risks were as expected for an antireflux surgical procedure, and the serious adverse event rate was acceptable, with no new risks identified. The totality of the evidence gathered in these rigorous clinical trials clearly demonstrates that the LINX Reflux Management System will positively impact the lives of people suffering from GERD, and the clinical evidence supports approval.
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**Terms and Abbreviations**

<table>
<thead>
<tr>
<th>acronym</th>
<th>explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GEJ</td>
<td>Gastroesophageal Junction</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastroesophageal Reflux Disease</td>
</tr>
<tr>
<td>GERD-HRQL</td>
<td>GERD-Health Related Quality of Life Questionnaire</td>
</tr>
<tr>
<td>IDE</td>
<td>Investigational Device Exemption</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-Treat population</td>
</tr>
<tr>
<td>LES</td>
<td>Lower esophageal sphincter</td>
</tr>
<tr>
<td>LTF</td>
<td>Lost to Follow-up</td>
</tr>
<tr>
<td>ODE</td>
<td>Office of Device Evaluation</td>
</tr>
<tr>
<td>CDRH</td>
<td>Center for Devices and Radiological Health</td>
</tr>
<tr>
<td>PMA</td>
<td>Premarket Approval Application</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton Pump Inhibitor</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>UADE</td>
<td>Unanticipated Adverse Device Effect</td>
</tr>
</tbody>
</table>
1.0 Overview of Gastroesophageal Reflux Disease and Current Treatment Options

1.1 Gastroesophageal Reflux Disease – A Sphincter Disorder

Gastroesophageal Reflux Disease (GERD) is the most prevalent gastrointestinal disease in the USA and probably the most important in terms of chronic debility, cancer risk and overall cost. In addition to painful or debilitating symptoms, GERD may result in mucosal injuries of the esophagus ranging from inflammation, erosions and ulcerations, to Barrett’s esophagus with its risk for adenocarcinoma. The pathogenesis of GERD is complex and multifactorial. Of primary importance is the gastroesophageal barrier that prevents the reflux of gastric juice into the esophagus. The barrier consists of a high pressure zone in the lumen of the distal most portion of the esophagus termed the lower esophageal sphincter (LES), with contributory effects from the diaphragm and phrenoesophageal ligament. The effectiveness of the LES as a barrier to reflux is dependent on its ability to resist opening in response to challenges of gastric distention.

1.2 Current Treatment Options for GERD

The primary therapy for GERD is medical management using proton pump inhibitors (PPIs) that suppress gastric acid secretion. PPI therapy is highly effective in healing esophagitis but less effective in controlling reflux-related symptoms. Multiple studies have shown symptom-control failure rates of up to 40% in patients with GERD. PPIs are also ineffectual in preventing severe regurgitation and non-acid reflux symptoms since acid suppression therapy does not improve the function of the barrier. As an acid suppressant medication, the expected pH normalization success rate while taking PPI therapy has been reported to be in the range of 50%.

Although generally safe, chronic PPI use may be associated with multiple side effects such as osteoporosis, aspiration pneumonia, C. difficile infection, electrolyte disturbances and detrimental interaction with other medication. Of further consideration, PPI therapy is approved for short durations of use only, even though most chronic GERD patients are taking PPIs daily with the expectation of life-long therapy.
At present the only alternative to medical therapy of GERD is antireflux surgery, typically Nissen fundoplication or a variation thereof. The Nissen fundoplication has recently been shown to yield equivalent long-term outcomes compared to PPI therapy; however, the use of this procedure is declining, due to its side effects including the inability to belch or vomit, increased flatulence, and a low incidence of persistent dysphagia. Standardization of the procedure has proven difficult despite decades of experience, and the procedure results in anatomic alterations that cannot be easily revised. Most referrals for fundoplication are typically reserved for patients with a large hiatal hernia or very advanced disease.

At present, there is no intermediary therapy between PPIs and fundoplication. As a result, there is a “Therapy Gap” which leaves patients in a treatment predicament: either accept life-long PPI therapy with insufficient symptom relief or commit to a fundoplication with its attendant side effects. An alternative treatment option is needed for these patients. An ideal treatment will be simple, standardized, and address the underlying physiologic defects. The results should produce definitive clinical relief of GERD related symptoms and esophageal injury. Importantly, this treatment should be safe, not altering existing anatomy or creating clinically significant side effects. For those patients who have a known pathologic defect of their LES, and an incomplete symptomatic response PPI therapy, life-long drug therapy may not be desirable treatment option. The LINX System is intended to address this unmet clinical need for GERD patients.

2.0 Device Description and Principles of Operation

2.1 Device and Accessory Description

The LINX Reflux Management System is intended for use in the those patients diagnosed with pathologic Gastroesophageal Reflux Disease (GERD) as defined by abnormal pH testing and who continue to have chronic GERD symptoms despite anti-reflux drug therapy. The LINX device is a permanent implant placed at the area of the Lower Esophageal Sphincter (LES) and is designed to augment a weak LES and minimize or eliminate GERD-related symptoms.
The LINX Reflux Management System is comprised of the following components:

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

The LINX Reflux Management System, hereafter called the LINX System or LINX device, consists of a series of titanium beads each with a magnetic core connected together 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 closed. During swallowing, the magnetic beads slide away from each other on the independent titanium wire “links” to allow esophageal distention as the bolus passes by.

The device is offered in multiple sizes to accommodate variations in esophageal size. The sizes are denoted by the model number (e.g., LS12 = 12 Bead Implant). An illustration of a “12 Bead” size LINX implant is provided in Figures 1 and 2.

Figure 1 – Illustration of Implant, Closed

Figure 2 – Illustration of Implant, Open
The LINX Reflux Management System Esophagus Sizing Tool, hereafter called the sizing tool, is a simple tool utilized to measure the external diameter of the esophagus at the implant site. This tool is used at the time of implant to guide the physician into choosing an appropriately sized device. The sizing tool is constructed similarly to the LINX device with a few exceptions that facilitate colorimetric referencing for proper sizing of the esophagus (Figure 3). Sizing is accomplished by wrapping the sizing tool around the outer esophagus in the area of the LES and aligning the marker bead (white bead) with a color bead. The color bead that aligns with the marker bead represents the size of device to implant (Figure 4). Each color represents a different size of device (Table 1).

**Figure 3 - Illustration of Sizing Tool**

![Image of Sizing Tool](image)

**Figure 4: Sizing of the Esophagus**

![Image of Sizing Procedure](image)
Table 1: Sizing Bead Color and Associated Device

<table>
<thead>
<tr>
<th>Bead Color</th>
<th>Associated Device (Bead Length)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre - Orange</td>
<td>10-Bead</td>
</tr>
<tr>
<td>Orange</td>
<td>11-Bead</td>
</tr>
<tr>
<td>Yellow</td>
<td>12-Bead</td>
</tr>
<tr>
<td>Green</td>
<td>13-Bead</td>
</tr>
<tr>
<td>Blue</td>
<td>14-Bead</td>
</tr>
<tr>
<td>Purple</td>
<td>15-Bead</td>
</tr>
<tr>
<td>1st Bead Post-Purple</td>
<td>16-Bead</td>
</tr>
<tr>
<td>2nd Bead Post-Purple</td>
<td>17-Bead</td>
</tr>
<tr>
<td>3rd Bead Post-Purple</td>
<td>18-Bead</td>
</tr>
</tbody>
</table>

2.2 Principles of Operation

The LINX Reflux Management System allows a surgeon, using existing laparoscopic techniques and instruments, to augment a weak sphincter and restore the barrier function of the lower esophageal sphincter (LES). The mechanism of action for the LINX device is to augment the sphincter’s capacity to resist gastric pressure by using magnetic forces. For abnormal reflux to occur following implantation of the LINX device, 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 magnetic bond between the beads is overcome by the higher pressures of peristaltic swallowing forces, and the device expands to accommodate a normal swallow (Figures 5-7).

Figure 5: LINX device preventing reflux
Figure 6: LINX device during swallowing
Figure 7: LINX is Non-Compressive
3.0 Non-Clinical Laboratory Studies

3.1 In-Vitro Bench Testing

In vitro (bench) testing was performed to ensure the safe and reliable performance of the LINX device. Testing including mechanical integrity and interference with other devices due to the static magnetic field present around the device. Results indicate the LINX System and the Esophagus Sizing Tool perform according to established specifications.

The LINX System and the Esophagus Sizing Tool were subjected to biocompatibility tests selected in accordance with the International Standards Organization (ISO) 10993-1, Biological Evaluation of Medical Devices, and FDA’s guidance, Blue Book Memorandum #G95-1. The biocompatibility tests were selected based on the nature and duration of body contact with the LINX (tissue/bone contacting permanent implant device-permanent, i.e. >30 days) and the Esophagus Sizing Tool (contacts breached or compromised tissue for a limited period, i.e., less than 24 hours). The biocompatibility studies were performed in compliance with Good Laboratory Practice (GLP) regulations, 21 CFR Part 58. The LINX device and Sizing Tool passed all biocompatibility tests, indicating that the materials and processes used to manufacture the devices are biocompatible and suitable for their intended use. Results of bench testing and biocompatibility testing are summarized in Table 2.

<table>
<thead>
<tr>
<th>Study/Test</th>
<th>Test Result</th>
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<tbody>
<tr>
<td>Mechanical Integrity Testing</td>
<td>Pass</td>
</tr>
<tr>
<td>Mechanical Tensile Strength</td>
<td>Pass</td>
</tr>
<tr>
<td>Mechanical Tensile Strength: Final Config. w/ Suture Knots</td>
<td>Pass</td>
</tr>
<tr>
<td>Mechanical Tensile Strength: Final Config. w/ Top Knots</td>
<td>Pass</td>
</tr>
<tr>
<td>Corrosion Test</td>
<td>Pass</td>
</tr>
<tr>
<td>Surface Analysis</td>
<td>Pass</td>
</tr>
<tr>
<td>Life Cycle Testing</td>
<td>Pass – 10 year simulated use</td>
</tr>
<tr>
<td>Magnetic Field Strength Testing</td>
<td>Pass</td>
</tr>
<tr>
<td>Biocompatibility Testing - LINX</td>
<td>Pass</td>
</tr>
<tr>
<td>Cytotoxicity - ISO 10993-5</td>
<td>Pass</td>
</tr>
</tbody>
</table>
### Study/Test

<table>
<thead>
<tr>
<th>Study/Test</th>
<th>Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitization - ISO 10993-10</td>
<td>Pass</td>
</tr>
<tr>
<td>Irritation/Intracutaneous Reactivity - ISO 10993-10</td>
<td>Pass</td>
</tr>
<tr>
<td>Systemic Toxicity - ISO 10993-11</td>
<td>Pass</td>
</tr>
<tr>
<td>Subchronic Toxicity, 14-day (repeat dose) - ISO 10993-11</td>
<td>Pass</td>
</tr>
<tr>
<td>Genotoxicity (Ames Assay) - ISO 10993-3</td>
<td>Pass</td>
</tr>
<tr>
<td>Biocompatibility Testing – Sizing Tool</td>
<td></td>
</tr>
<tr>
<td>Systemic Toxicity - ISO 10993-11</td>
<td>Pass</td>
</tr>
<tr>
<td>Subchronic Toxicity, 14-day (repeat dose) - ISO 10993-11</td>
<td>Pass</td>
</tr>
<tr>
<td>Irritation/Intracutaneous Reactivity - ISO 10993-10</td>
<td>Pass</td>
</tr>
<tr>
<td>Systemic Toxicity: Acute Systemic Injection - ISO 10993-11</td>
<td>Pass</td>
</tr>
</tbody>
</table>

---

### 3.2 Animal Studies

Pre-clinical evaluation of the LINX System in a chronic GLP animal study showed that the LINX System functioned as intended and histological findings were unremarkable and consistent with a typical foreign body response. Fibrous formation around the LINX beads was thin and flexible so swallow function and magnetic strength for closing and opening of the beads was preserved. The results of the study indicated that the device was safe and it was shown to actuate as expected.

A chronic animal study was conducted to assess the safety and the design of the LINX Reflux Management System. The study was conducted in compliance with Good Laboratory Practice (GLP) per 21 CFR 58. In the GLP study, twenty-five (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 based on the time of sacrifice, which occurred at 42 (2 groups), 91, 182, and 365 days post-implant.

Successful balloon actuations to simulate swallowing (beads opening) and ability of magnetic forces to return to resting state (beads closed) were obtained for all twenty-five (25) animals at all study time points. At sacrifice, all animals had devices encapsulated in fibrous tissue and, when evaluated histologically, the surrounding cells appeared stable. Healing appeared to be complete by 3 months and the
internal esophagus was noted as unremarkable and the LINX device healed well into the external esophagus. Gross necropsy examination showed normal organs with minimal to moderate adhesions near the implant. The results of the study indicate that the device was safe, and it was shown to actuate as expected before, during and after the healing process.

4.0 Overview of Clinical Studies
Two prospective, non-randomized clinical trials were conducted in the United States and Europe under IDE G060172 to support the safety and effectiveness of the LINX Reflux Management System. The first was a feasibility trial, conducted at two (2) investigational centers in the United States and two (2) investigational sites in Europe. A total of 44 subjects were implanted with the LINX device to evaluate the safety of the device and collect preliminary performance information regarding its ability to reduce the symptoms of GERD by reinforcing the function of the lower esophageal sphincter (LES). The safety and performance observed in this trial led to the initiation of the pivotal trial.

The second was a pivotal, multi-center, single arm clinical trial that was conducted in the United States and Europe where one hundred (100) subjects were implanted with the LINX device at fourteen (14) implanting sites. The pivotal trial evaluated the safety and effectiveness of the LINX Reflux Management System to augment the barrier function of the LES in the treatment of GERD for those subjects diagnosed with pathological GERD as defined by abnormal pH testing and who continue to have chronic GERD symptoms despite anti-reflux drug therapy.

The design and conduct of LINX Clinical Trials involved using subjects as their own control. Comparative treatments were considered as randomized controls; however, a self-controlled study was deemed the best option for the following reasons:

- Subjects had already demonstrated chronic GERD symptoms despite PPI therapy and were seeking an alternative treatment. Randomizing to continued PPI use was viewed as a significant barrier to enrollment by our
consulting physicians, and blinding subjects and physicians to the treatment assignment was not practical or possible.

- **Fundoplication** was considered for a randomized control, but:
  - Fundoplication is generally reserved for more advanced GERD patients (i.e. large hernias and advanced mucosal injury); and therefore, a different target population than the LINX Study.
  - Fundoplication is associated with significant variations in technique, making standardization of the procedure under a study protocol in multiple study centers not practical.
  - Fundoplication was an available treatment option outside of the trials, and an option subjects had chosen not to pursue. It was unlikely that patients would consent to the possibility of randomization to a fundoplication.

In addition, other considerations in favor of a subject as their own control to provide valid scientific information included:

- Quantitative diagnosis of the subject population verified that the subjects had the condition to be treated and that the condition was chronic and would not improve without treatment, and
- Standardized and objective performance criteria, in the form of esophageal pH testing, and esophagitis classification ensured an accurate assessment of treatment effects.

In the absence of appropriate direct comparators, determining the acceptability of the risk benefit ratio associated with the LINX System requires sound medical judgment. Such judgments should be based on the totality of evidence with respect to clinical outcomes. Moreover, the LINX System successfully addresses the treatment goals for such devices established by the Society of American Gastrointestinal Endoscopic Surgeons (SAGES), which are:

- elimination of symptoms
- healing of esophagitis
- prevention of complications
- maintenance of remission
The clinical trials for the LINX device clearly established that the probable benefits of treatment with the device outweigh the probable risks.

5.0 Feasibility IDE Trial

5.1 Feasibility IDE Trial Design
The Feasibility IDE trial was an observational, prospective, non-randomized, open label study conducted at four (4) investigational centers. Forty-four (44) subjects with confirmed GERD and incomplete symptom response to daily proton pump inhibitors (PPIs) were implanted with the LINX device. In this single-arm study, subjects served as their own treatment control by measuring improvement from their baseline condition. The procedure was performed laparoscopically. All subjects were successfully implanted without conversion to fundoplication at time of implant. The primary safety objective of the feasibility study was to evaluate the incidence of adverse events. The performance objectives of the study were to monitor the improvement of GERD symptoms up to 60 months post implant and to optimize the implant technique. GERD symptoms were assessed by subjective measurements using the GERD-HRQL and PPI use. LES function was characterized by objective measurements including 24 hour pH profile, manometry/motility, and barium esophagram. Follow-ups occurred at discharge, 2 weeks, 3, 6, and 12 months, then annually through 5 years.

5.2 Feasibility Study Safety and Effectiveness Results
A total of 44 subjects were implanted with the LINX device. A total of 24/44 (54.5%) subjects experienced adverse events related to the device and/or procedure. The most common adverse event was dysphagia (22 events in 20 subjects). To date, no device migrations or erosions have been reported. Serious adverse events (SAEs) occurred in two (2) subjects. One subject experienced dysphagia initially following the procedure and presented with ongoing dysphagia at the 6-month follow-up. The decision was made to remove the device. 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 1 month post-explant. This subject subsequently had a fundoplication procedure. The other subject experienced chest pain resulting in hospitalization 22 days after the implant procedure. This event was resolved within 55 days of implant. Two device removals have been performed for reasons other than an adverse event. One 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. Although the subject’s GERD symptoms were well controlled with the LINX device, the Investigator complied with this request and removed the device 468 days post-implant without incident. Subjects continue to be followed for adverse events and no unanticipated adverse device effects have been reported.

The primary performance objectives of the feasibility clinical investigation were to monitor improvements in the subject’s GERD symptoms by using the GERD-HRQL (Health Related Quality of Life Scale) and reduction in PPI use. In addition, pH monitoring was used as an objective, physiological measurement. Improvement in GERD-HRQL scores by ≥50% occurred in at 97.4% (38/39) of subjects at 12 months, 88.6% (31/35) at 24 months and 96.3% (26/27) at 36 months. The percentage of subjects reporting being “satisfied” with their present condition was 87.2% (34/39) at 12 months, 80.0% (29/35) at 24 months, and 92.6% (25/27) at 36 months. Reduction in 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. 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. Please note: pH monitoring is not performed in US subjects beyond the 12-month follow-up.
6.0 Pivotal IDE Trial

6.1 Pivotal IDE Trial Design

The Pivotal IDE trial was a prospective, multi-center, single-arm study with subjects serving as their own treatment control. The purpose of the study was to evaluate the safety and effectiveness of the LINX device in the treatment of GERD through augmentation of the barrier function of the LES. The trial was conducted at 16 sites in the United States and Europe, 14 of which had subjects that met the eligibility requirements and were implanted with the investigational device. Ninety-six (96) subjects were implanted in the United States and four (4) in Europe. All enrolled subjects had abnormal esophageal pH and chronic GERD symptoms despite PPI therapy prior to implant. A total of 100 subjects were implanted. Among subjects completing follow-up, 98 subjects have been followed for one year, and 90 subjects have been followed for two years.

6.2 Inclusion Criteria

Enrollment into the pivotal trial was limited to subjects who met the following 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 for 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 absence of PPI therapy (minimum 7 days).

8. If the subject is of child bearing potential 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.

### 6.3 Exclusion Criteria

Subjects were not permitted to enroll in the pivotal trial if they met any of the following 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 follow-up 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.

### 6.4 Follow-up Schedule

Prior to treatment, all subjects underwent a medical history and physical exam, esophagogastrroduodenoscopy (EGD), barium esophagram, esophageal manometry, and 48-hour ambulatory pH study (following a 7 day PPI medication wash out period). Additionally, each subject completed the GERD-HRQL (on and off PPI medication) and Foregut Symptom questionnaires. Follow-up per protocol was performed at discharge, 1 week, 3 months, 6 months, 12 months and 24 months. Assessment for the efficacy endpoint was performed at 12 months and assessments for secondary efficacy endpoints were performed at 12 and 24 months (±60 days) from implant date.
6.5 Accountability of the Study Cohort

Informed Consent I (ICI) was signed by 257 subjects. Screening failures occurred in 154 of these subjects. Informed Consent II 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 for the following reasons: in the case of two subjects, the limit of 100 implants had been reached; and the other subject was determined to have an allergy to nickel. The site inadvertently had the subject sign IC II before full eligibility was determined. The Intent-to-Treat Group and Treated Group consisted of 103 and 100 subjects, respectively. The endpoint analysis was based on the Treated Group.

Overall, visit compliance was excellent. Two explanted subjects were withdrawn prior to the 12 month visit. Ninety-eight subjects were still enrolled 12 months post implant. No subjects were lost to follow-up, for a compliance rate of 100% (reference Table 3.)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Number Withdrawn</th>
<th>Number Expected</th>
<th>Number Visits</th>
<th>Compliance %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Operative</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100.0%</td>
</tr>
<tr>
<td>Procedure</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100.0%</td>
</tr>
<tr>
<td>Discharge</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100.0%</td>
</tr>
<tr>
<td>Week 1</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100.0%</td>
</tr>
<tr>
<td>3 Months</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100.0%</td>
</tr>
<tr>
<td>6 Months</td>
<td>1</td>
<td>99</td>
<td>99</td>
<td>100.0%</td>
</tr>
<tr>
<td>12 Months</td>
<td>2</td>
<td>98</td>
<td>98</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Visit compliance at 24 month was excellent as well with a compliance rate of 95% (Table 4). Reasons for withdrawal or non-completion are provided in Table 5.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Total Number Implanted</th>
<th>Number Explanted Prior to 24M</th>
<th>Number Expected at 24M</th>
<th>Number Withdrawn / LTF at 24M</th>
<th>Number Non-Completions</th>
<th>Number Visits at 24M</th>
<th>Compliance % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 Months</td>
<td>100</td>
<td>5</td>
<td>95</td>
<td>2</td>
<td>3</td>
<td>90</td>
<td>94.7% (90/95)</td>
</tr>
</tbody>
</table>
Table 5: Reasons for Withdrawals/Non-Completions Reasons

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost to Follow-up</td>
<td>1</td>
</tr>
<tr>
<td>Declined re-consent to continued follow-up</td>
<td>1</td>
</tr>
<tr>
<td>Subjects were contacted and did not ask to be withdrawn but have not complied with scheduled visit attendance</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
</tr>
</tbody>
</table>

6.6 Study Population Demographics and Baseline Parameters

Table 6 displays baseline summary statistics for selected demographics and Body Mass Index (BMI). The average age of subjects implanted was 50.4 years. Fifty-two percent (52%) were male and 48% female.

Table 6: Baseline Demographics and Medical History

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Mean±SD (Median)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>100</td>
<td>50.4±12.4 (53.0)</td>
<td>18.3, 74.7</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>100</td>
<td>27.9±3.4 (27.9)</td>
<td>19.8, 34.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52.0% (52/100)</td>
</tr>
<tr>
<td>Female</td>
<td>48.0% (48/100)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian/Non-Hispanic</td>
<td>96.0% (96/100)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.0% (3/100)</td>
</tr>
<tr>
<td>Other</td>
<td>1.0% (1/100)</td>
</tr>
<tr>
<td>BMI Class</td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;25)</td>
<td>19.0% (19/100)</td>
</tr>
<tr>
<td>Overweight (≥25 and &lt;30)</td>
<td>55.0% (55/100)</td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>26.0% (26/100)</td>
</tr>
</tbody>
</table>
The baseline evaluations established the basis for assessing response to treatment post-implant for individual subjects. Subjects entered the study with abnormal esophageal pH, daily heartburn and regurgitation, and daily use of PPI therapy. Subjects showed an incomplete response to PPI therapy as evidenced by a partial, but incomplete response to PPI therapy measured by the GERD-HRQL Questionnaire, where the Off PPI therapy mean score was 26.6 and the On PPI therapy mean score was 12.0 (Table 7). Study subjects had a long-standing history of GERD (mean duration 12.8 years) and long-term use of PPI medications (mean duration of 6.3 years), as reported in Table 8.

**Table 7: GERD Medical History**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily PPI Use %</td>
<td>100%</td>
</tr>
<tr>
<td>GERD-HRQL Total Score</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td>%Satisfied</td>
<td></td>
</tr>
<tr>
<td>Off PPI</td>
<td>26.6±6.6</td>
</tr>
<tr>
<td>27.0 (11, 47)</td>
<td></td>
</tr>
<tr>
<td>0.0% (0/100)</td>
<td></td>
</tr>
<tr>
<td>On PPI</td>
<td>12.0±6.8</td>
</tr>
<tr>
<td>11.0 (0, 28)</td>
<td></td>
</tr>
<tr>
<td>13.0% (13/100)</td>
<td></td>
</tr>
<tr>
<td>Total % pH Time &lt;4</td>
<td>11.6±4.7</td>
</tr>
<tr>
<td>Median (range)</td>
<td>10.9 (4.8, 25.4)</td>
</tr>
<tr>
<td>Esophagitis (%) Grade A or B</td>
<td>40% (40/100)</td>
</tr>
<tr>
<td>Heartburn - Frequency/week</td>
<td>78.6±141.5</td>
</tr>
<tr>
<td>Median (range)</td>
<td>35.0 (0, 700)</td>
</tr>
<tr>
<td>Regurgitation – Frequency/week</td>
<td>27.9±61.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>7.0 (0, 420)</td>
</tr>
</tbody>
</table>

**Table 8: Duration of GERD and PPI Use**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Mean±SD (Median)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI Use (years)</td>
<td>100</td>
<td>6.3±4.8 (4.8)</td>
<td>0.2⁻¹, 20.0</td>
</tr>
<tr>
<td>GERD (years)</td>
<td>100</td>
<td>12.8±9.2 (10.0)</td>
<td>0.8, 40.0</td>
</tr>
</tbody>
</table>

¹ One subject went on a short term course of PPI therapy for the study. The subject had been taking H2 blockers instead of PPI medications for GERD as prescribed by primary care physician.
6.7 Procedure Information

The 100 subjects who proceeded to surgery were all successfully implanted with the LINX device by laparoscopy and completed the procedure with no cross-over to an open surgical technique or Nissen fundoplication. No intra-operative or discharge serious adverse events were reported. The average procedure duration was 39 minutes, defined as the time from all ports were in place, to when the first port was removed. Half the subjects (50/100) were discharged the same day as surgery, and the other half (50/100) were discharged the next day. No subjects required extended hospitalization due to an adverse event. The total number of implants performed by academic sites compared to community-based sites was quite evenly distributed. Academic sites performed 51 implants and community sites performed 49 implants.

6.8 Safety Objective

The primary safety objective was to estimate the rate of serious device and/or procedure related adverse events with a sufficient level of precision to inform a risk/benefit assessment. The targeted precision level expressed in the protocol (6.6%) was based on an assumption of observing an event rate of 10%. This level of precision was sufficient to assess the safety of the device and procedure. Safety outcomes were carefully assessed throughout the study period. The procedure was carefully monitored for complications and time to complete. The length of stay was also documented. Any changes to the LINX device after implant such as migration or erosion were monitored through endoscopy, barium esophagrams and chest x-rays. Changes in subject weight were followed and any changes greater than 10% were discussed with the Investigator. Adverse events of any type were monitored throughout the study period.
6.9 Safety Results

A total of nine (9) serious device and/or procedure related adverse events occurred in six (6) subjects. In three (3) subjects, an adverse event of dysphagia was serious as it resulted in the explant of the LINX device. Following explant, the dysphagia resolved with no sequelae in all cases. Two (2) subjects were briefly hospitalized in the early post-operative period due to nausea or vomiting, which resolved without further treatment. Another subject was hospitalized twice during the course of the study, once for pain of unknown etiology and another time for explant of the device related to vomiting of unclear causality, but possibly related per CEC adjudication. Related SAEs as reported by Investigators and adjudicated by the CEC are displayed in Table 10. No deaths, device erosions, device migrations occurred during the study, and no Unanticipated Adverse Device Effects were reported.

Table 9: Related Serious Adverse Events at 12 Months and 24 Months

<table>
<thead>
<tr>
<th>SAE</th>
<th>Number of Events at 12M</th>
<th>Number of Events at 24M</th>
<th>% Subjects (Number of Subjects/Total)</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious device and/or procedure related adverse event</td>
<td>9</td>
<td>0</td>
<td>6.0% (6/100)</td>
<td>2.2%, 12.6%</td>
</tr>
</tbody>
</table>

1Includes one SAE with adjudicated relationship to device/procedure of Unknown

Table 10: Related SAEs as Reported by Investigators and Adjudicated by the CEC

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>As reported by the investigator</th>
<th>As adjudicated by the CEC</th>
<th>Total as reported by investigator or by the CEC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (n)</td>
<td>Subjects % (n)</td>
<td>Events (n)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>3</td>
<td>3% (3)</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1% (1)</td>
<td>2</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>1% (1)</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
</tr>
</tbody>
</table>

1Causality reported as unknown
2CEC adjudicated nausea AE as related whereas Investigator did not
3Investigator reported AE as related whereas CEC did not
At 12 months, there were a total of 310 events in 88 subjects. Of these, 162 events were considered related or unknown causality (Table 11). Of the related adverse events, dysphagia was the most frequently reported event (76 events in 68 subjects) followed by pain (21 events in 20 subjects). Both dysphagia and pain are anticipated following anti-reflux surgery. Dysphagia was reported as mild in 71% (54/76) of events.

Dysphagia following antireflux surgery is common and expected in the early post-operative period, largely due to edema and inflammation. Study subjects had varying levels of dysphagia following LINX implantation. As required by the protocol, any complaint of difficulty swallowing, regardless of clinical significance, was reported as an adverse event (AE). It is important to note that subjects were encouraged to begin eating a normal diet immediately after the LINX implant procedure. This approach differs significantly from fundoplication procedures, where the diet is slowly advanced over a span of a few weeks or months, starting with only liquids and then soft foods and eventually solids. The dysphagia reported during the LINX studies was generally mild and did not prevent subjects from eating a normal diet.

In almost all cases, the dysphagia has an early onset and self resolves within a few months. Severity of adverse events, beyond 6 months, are all classified as mild, with no incidence of moderate or severe. Persistent dysphagia can be managed with endoscopic dilations. Most subjects who had a dilation improved or resolved their dysphagia. Persistent dysphagia, not responsive to dilation, may be resolved by explant. Overall, 3% of pivotal trial participants had their device explanted for the primary reason of dysphagia. All explant procedures were safely performed laparoscopically without clinical sequelae and led to resolution of the dysphagia.

Additional safety assessments performed at 12 months did not identify any significant issues. No device erosions or migrations were identified by endoscopy or chest/abdominal x-rays. Normal swallow function by barium esophagram was seen in 97% of subjects. Manometry/motility showed mean % effective liquid swallows was 85% at 12 months (within normal range). Mean distal amplitude, a measure of
peristaltic pressure in the esophagus, was in the normal range at 12 months (84.5 mmHg). Overall, these additional safety assessments provided further support that treatment with the LINX device does not pose any significant safety risk, and there was no evidence of long-term adverse effects on the esophagus related to the LINX device.

Table 11: Related or Unknown Adverse Events at 12 Months

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Related or Unknown</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AEs (n)</td>
<td>Subj. % (n)</td>
<td>AEs (n)</td>
<td>Subj. % (n)</td>
</tr>
<tr>
<td>Total</td>
<td>162</td>
<td>76% (76)</td>
<td>108</td>
<td>65% (65)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>76</td>
<td>68% (68)</td>
<td>54</td>
<td>49% (49)</td>
</tr>
<tr>
<td>Pain</td>
<td>25</td>
<td>24% (24)</td>
<td>8</td>
<td>8% (8)</td>
</tr>
<tr>
<td>Stomach Bloating</td>
<td>15</td>
<td>14% (14)</td>
<td>13</td>
<td>12% (12)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>7% (7)</td>
<td>4</td>
<td>3% (3)</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>8</td>
<td>8% (8)</td>
<td>4</td>
<td>4% (4)</td>
</tr>
<tr>
<td>Other: HICCUPS</td>
<td>8</td>
<td>8% (8)</td>
<td>7</td>
<td>7% (7)</td>
</tr>
<tr>
<td>Inability to belch or vomit</td>
<td>6</td>
<td>6% (6)</td>
<td>5</td>
<td>5% (5)</td>
</tr>
<tr>
<td>Other: DECREASED APPETITE</td>
<td>4</td>
<td>4% (4)</td>
<td>4</td>
<td>4% (4)</td>
</tr>
<tr>
<td>Other: BELCHING</td>
<td>2</td>
<td>2% (2)</td>
<td>2</td>
<td>2% (2)</td>
</tr>
<tr>
<td>Other: FLATULENCE</td>
<td>2</td>
<td>2% (2)</td>
<td>2</td>
<td>2% (2)</td>
</tr>
<tr>
<td>Other: WEIGHT LOSS</td>
<td>2</td>
<td>2% (2)</td>
<td>2</td>
<td>2% (2)</td>
</tr>
<tr>
<td>Other: FOOD IMPACTION</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Other: GLOBUS SENSATION</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Other: IBS/DYSPEPSIA</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Other: REGURGITATION OF STICKY MUCUS</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Other: UNCOMFORTABLE FEELING IN CHEST</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
At 24 months, the clinical data showed continued safety and minimal risk. No serious device and/or procedure related adverse events were reported. No device erosions or migrations were reported. One subject, with recurrent symptoms of GERD, had the device electively removed without complications and underwent a Nissen fundoplication at the time of device removal. Related or unknown adverse events that are new since the 12 month clinical study report are summarized in Table 12 and included one related event for each of the following: odynophagia, inability to vomit, and increased gas. Additionally, there was one event of mild pain with unknown causality. Overall, risks of the LINX device and procedure have been consistent with the established risks expected following current antireflux surgery.

Table 12: Summary of New Adverse Events – Related or Unknown

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AEs (n)</td>
<td>Subj. % (n)</td>
<td>AEs (n)</td>
</tr>
<tr>
<td>Pain</td>
<td>4</td>
<td>4% (4)</td>
<td>0</td>
</tr>
<tr>
<td>Inability to belch or vomit</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
</tr>
<tr>
<td>Other: Increased gas per rectum</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

6.10 Effectiveness Objectives

**Primary Effectiveness Endpoint**

The primary endpoint was a reduction in acid exposure based on a comparison of a subject’s baseline pH test with this finding at 12 months post LINX implantation. Success on the subject level was defined as normalization of acid (pH<4 for ≤4.5% of time) or reduced total time (pH<4) by at least 50% relative to baseline measurements. The tested hypothesis was that the lower one-sided 97.5% confidence bound would indicate that the treatment success rate is greater than 60%.
**Secondary Effectiveness Endpoints**

There were two secondary endpoints in the Pivotal trial. The first of these assessed improvement in GERD symptoms defined by the validated GERD-HRQL Questionnaire. Individual subject success was defined as a reduction of ≥ 50% in the total GERD-HRQL score at 12 months post implantation as compared to a subject’s baseline score Off PPI therapy. Successful evaluation of this endpoint occurred if the lower one-sided 97.5% confidence bound showed that the individual success rate of the treatment group exceeds 60%.

The second secondary endpoint assessed reduction in the use of PPI medications. All subjects consented to the study were using PPI drugs on a daily basis and were documented for incomplete relief of their GERD symptoms while on these drugs. It was expected that LES augmentation from the LINX device would eliminate this daily dependence on PPI drugs and maintain control of GERD related symptoms. Individual subject success was defined as a reduction from baseline in PPI daily use by ≥ 50% at 12 months post implantation as compared to the subject’s baseline PPI use. Successful evaluation of this endpoint occurred if the lower one-sided 97.5% confidence bound showed that the individual success rate exceeds 60%. Testing of the secondary endpoint hypotheses was to be dependent on the achievement of success in the primary effectiveness endpoint.

**6.11 Effectiveness Results**

In accordance with the goals of The Society of American Gastrointestinal Endoscopic Surgeons, it was important to evaluate the ability of the LINX System to significantly reduce reflux symptoms and heal mucosal injuries leading to esophagitis. The device needs to do this in a way that minimizes potential side effects; such as gas bloat, impaired swallow function, and an impaired ability to vomit and belch. All of these factors were assessed carefully through the GERD-HRQL and Foregut Questionnaires and adverse event reporting.
Also important, was the degree of overall subject satisfaction. It was the existence of patient dissatisfaction with their condition, under treatment with PPI therapy, which drove subjects to seek a surgical alternative. Thus, it was critical to evaluate the effectiveness of the LINX procedure in improving overall satisfaction.

At 12 months, 98 of 100 subjects had a follow-up visit (in a few instances, some of the subjects declined to submit to the uncomfortable pH monitoring or manometry, so not all required assessments are available for all subjects). At 24 months, 95 subjects continued to have the device implanted, and 90 completed the 24-month follow-up visit.

**Esophageal pH testing**

Esophageal pH testing at 12 months was completed by 96 of the 100 implanted subjects. The mean total acid exposure time was reduced from 11.6% at baseline to 5.1% at 12 months, a 56% reduction. Also, 90% of treated subjects (86/96) were able to reduce their total acid exposure time. The individual patient success rate for the primary endpoint was 67% (64/96) for subjects who completed pH testing at 12 months. The overall success rate for all treated subjects was 64% (64/100), with a corresponding lower 97.5% confidence bound of 54%. This lower confidence bound is below the pre-specified performance goal of 60%, but still reflects a clinically important improvement. This outcome is satisfactory considering the overall strength of other effectiveness measures and low risk of the device compared to alternative therapies.

All pH tests performed at baseline and at follow-up in the Pivotal Study were performed with Bravo pH monitoring (Given Imaging, Duluth, GA). As detailed in Table 13, all six components of the pH test demonstrate a significant reduction in acid exposure following LINX implantation.
Table 13: pH Parameters of Esophageal Acid Exposure

<table>
<thead>
<tr>
<th>DeMeester Components</th>
<th>Normal Values¹</th>
<th>Baseline N=100</th>
<th>12 Months N=96²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time pH&lt;4 (%)</td>
<td>5.3</td>
<td>11.6±4.7 (10.9)</td>
<td>5.1±4.8 (3.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=100</td>
<td>N=96</td>
</tr>
<tr>
<td>Upright time pH&lt;4 (%)</td>
<td>6.9</td>
<td>14.0±7.2 (12.7)</td>
<td>6.5±5.8 (4.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=100</td>
<td>N=96</td>
</tr>
<tr>
<td>Supine Time pH&lt;4 (%)</td>
<td>6.7</td>
<td>7.8±7.2 (6.0)</td>
<td>2.9±5.8 (0.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=98</td>
<td>N=95</td>
</tr>
<tr>
<td>Number of Episodes pH&lt;4</td>
<td>36.8</td>
<td>175.0±81.7 (161.0)</td>
<td>82.8±67.6 (67.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=100</td>
<td>N=96</td>
</tr>
<tr>
<td>Number of Episodes &gt; 5 minutes</td>
<td>1.2</td>
<td>12.4±6.7 (12.0)</td>
<td>6.1±6.8 (4.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=99</td>
<td>N=96</td>
</tr>
<tr>
<td>Longest Episode (min)</td>
<td>N/A</td>
<td>37.4±24.4 (29.0)</td>
<td>19.7±20.9 (13.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=99</td>
<td>N=96</td>
</tr>
<tr>
<td>DeMeester Score</td>
<td>N/A</td>
<td>41.0±16.3 (36.6)</td>
<td>18.7±17.3 (13.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=97</td>
<td>N=95</td>
</tr>
</tbody>
</table>

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

**GERD-HRQL Results**

The study protocol required the GERD-HRQL questionnaire to be completed at baseline and then at 3, 6 and 12 months following LINX implantation. At baseline, the GERD-HRQL questionnaire was completed twice, once while on PPIs and then once again after PPIs had been stopped for at least 7 days. Symptom improvement defined by the GERD-HRQL questionnaire, following the LINX procedure, demonstrated a significant improvement in all assessments. Importantly, it can be seen that this improvement was shown relative to both baseline off and on PPI values. The mean total score at baseline was 26.6 Off PPI compared to 3.8 off PPI at 12 months and 4.3 off PPI at 24 months. The proportion of subjects achieving at least a 50% reduction from baseline was 92%, with corresponding lower 97.5% confidence bound of 84.8% - far exceeding the pre-specified performance goal of 60%. Table 14 reports GERD-HRQL total scores and mean reduction from baseline by visit.
Table 14: Mean GERD-HRQL Total Score and Mean Reduction from Baseline by Visit

<table>
<thead>
<tr>
<th>Visit</th>
<th>N</th>
<th>Mean±SD (Median)</th>
<th>Range Min, Max</th>
<th>N</th>
<th>Mean±SD (Median)</th>
<th>Range Min, Max</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline: Off PPI</td>
<td>100</td>
<td>26.6±6.6 (27.0)</td>
<td>11.0, 47.0</td>
<td>95</td>
<td>22.8±7.9 (23.0)</td>
<td>-2.0, 45.0</td>
<td>21.2, 24.4</td>
</tr>
<tr>
<td>Baseline: On PPI</td>
<td>100</td>
<td>12.0±6.8 (11.0)</td>
<td>0.0, 28.0</td>
<td>95</td>
<td>85.4±18.9 (90.5)</td>
<td>-7.1, 100.0</td>
<td>81.6, 89.3</td>
</tr>
<tr>
<td>12-Month</td>
<td>95</td>
<td>3.8±5.0 (2.0)</td>
<td>0.0, 30.0</td>
<td>95</td>
<td>8.0±7.5 (7.0)</td>
<td>-10.0, 26.0</td>
<td>6.5, 9.5</td>
</tr>
<tr>
<td>Reduction: Off</td>
<td>95</td>
<td>4.3±5.4 (2.0)</td>
<td>0.0, 27.0</td>
<td>90</td>
<td>22.2±8.6 (23.5)</td>
<td>-12.0, 45.0</td>
<td>20.4, 24.0</td>
</tr>
<tr>
<td>% Reduction: Off</td>
<td>95</td>
<td></td>
<td></td>
<td>90</td>
<td>82.4±25.4 (89.7)</td>
<td>-80.0, 100.0</td>
<td>77.1, 87.8</td>
</tr>
<tr>
<td>Reduction: On</td>
<td>90</td>
<td></td>
<td></td>
<td>90</td>
<td>7.5±7.7 (8.0)</td>
<td>-21.0, 25.0</td>
<td>5.9, 9.1</td>
</tr>
</tbody>
</table>

Elimination or Reduction of PPI Use

A primary indicator for any interventional GERD treatment is to provide symptom relief without daily PPI dependence. Subjects from the pivotal trial were on 100% daily use of PPI medication at baseline. This daily dependence was reduced to 9% at 12 months and 8% at 24 months post LINX implantation (see Table 15). The percentage of subject meeting the goal of 50% reduction in daily use of PPIs was 93% at 12 months, with a corresponding lower 97.5% confidence interval bound of 86.1%. The lower confidence bound far exceeds the pre-specified performance goal of 60%.

Table 15: PPI Use at Baseline, 12 Months and 24 Months

<table>
<thead>
<tr>
<th>PPI Use</th>
<th>Baseline (%)</th>
<th>12 Month (%)²</th>
<th>24 Month (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=100</td>
<td>N=97</td>
<td>N=89</td>
</tr>
<tr>
<td>None</td>
<td>0.0% (0/100)</td>
<td>88.7% (86/97)</td>
<td>86.7% (78/90)</td>
</tr>
<tr>
<td>PRN¹</td>
<td>0.0% (0/100)</td>
<td>2.1% (2/97)</td>
<td>5.6% (5/90)</td>
</tr>
<tr>
<td>QD¹</td>
<td>64.0% (64/100)</td>
<td>7.2% (7/97)</td>
<td>6.7% (6/90)</td>
</tr>
<tr>
<td>BID¹</td>
<td>35.0% (35/100)</td>
<td>2.1% (2/97)</td>
<td>1.1% (1/90)</td>
</tr>
<tr>
<td>TID¹</td>
<td>1.0% (1/100)</td>
<td>0.0% (0/97)</td>
<td>0.0% (0/90)</td>
</tr>
</tbody>
</table>

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

An important clinical measure of GERD is the extent of mucosal injury from reflux. Acid exposure testing is a surrogate only to the risk of esophagitis and mucosal injury. At baseline, 60% of subjects had no esophagitis. At 12 and 24 months, respectively, 88% (85/97) and 89% (19/89) of the subjects were free of any esophagitis. Grade B, the most advanced form of esophagitis allowed in the study population, decreased from 18% (18/100) of subjects at baseline to 1% and 3% at 12 and 24 months, respectively, following LINX implant (see Table 16).

<table>
<thead>
<tr>
<th>Esophagitis Grade</th>
<th>Baseline % (n/N)</th>
<th>Month 12 % (n/N)</th>
<th>Month 24 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>60.0% (60/100)</td>
<td>87.6% (85/97)</td>
<td>88.7% (79/89)</td>
</tr>
<tr>
<td>Grade A¹</td>
<td>22.0% (22/100)</td>
<td>10.3% (10/97)</td>
<td>7.9% (7/89)</td>
</tr>
<tr>
<td>Grade B¹</td>
<td>18.0% (18/100)</td>
<td>1.0% (1/97)</td>
<td>3.4% (3/89)</td>
</tr>
<tr>
<td>Grade C¹</td>
<td>0.0% (0/100)</td>
<td>0.0% (0/97)</td>
<td>0.0% (0/89)</td>
</tr>
<tr>
<td>Grade D¹</td>
<td>0.0% (0/100)</td>
<td>1.0% (1/97)</td>
<td>0.0% (0/89)</td>
</tr>
</tbody>
</table>

¹Reference of LA Classification for Esophagitis: Grade A=Mucosal break < 5 mm in length; Grade B= Mucosal break > 5mm; Grade C=Mucosal break continuous between > 2 mucosal folds; Grade D= Mucosal break >75% of esophageal circumference

**Regurgitation Severity and Frequency**

The symptom of heartburn is largely associated with acid exposure in the esophagus. This symptom is the primary target of acid suppression therapy in the form of PPI drugs. As discussed, reflux disease is a mechanical disorder of the GEJ barrier which allows the abnormal reflux of gastric contents. As PPI drugs only reduce acid from the stomach, the mechanism of reflux continues. This often results in the symptom of regurgitation. Regurgitation is the sensation from gastric fluids refluxing into the esophagus, the airway and even into the mouth. At baseline, 91% (91/100) of subjects experienced regurgitation of varying severity at a mean frequency of 28 times per week. At 12 and 24 months post LINX implantation, this mean frequency was reduced to 1 time per week and the prevalence of regurgitation dropped from 91% to 22% of subjects. Most importantly, severe regurgitation, defined as constant and presence of aspirations, dropped from 13% at baseline to 1% at 12 and 24 months post LINX implantation (see Table 17).
Table 17: Regurgitation Severity and Frequency

<table>
<thead>
<tr>
<th>Severity</th>
<th>Baseline % (n/N)</th>
<th>Month 12 % (n/N)</th>
<th>Month 24 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>9.0% (9/100)</td>
<td>78.9% (75/95)</td>
<td>77.8% (70/90)</td>
</tr>
<tr>
<td>Mild – After straining and/or large meals</td>
<td>34.0% (34/100)</td>
<td>18.9% (18/95)</td>
<td>21.1% (19/90)</td>
</tr>
<tr>
<td>Moderate – Predictable with position change, straining or lying down</td>
<td>44.0% (44/100)</td>
<td>1.1% (1/95)</td>
<td>0.0% (0/90)</td>
</tr>
<tr>
<td>Severe - Constant regurgitation, presence of aspiration into lungs</td>
<td>13.0% (13/100)</td>
<td>1.1% (1/95)</td>
<td>1.1% (1/90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from BL</th>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>83.2% (79/95)</td>
<td>84.4% (76/90)</td>
</tr>
<tr>
<td>Same</td>
<td>15.8% (15/95)</td>
<td>13.3% (12/90)</td>
</tr>
<tr>
<td>Worsened</td>
<td>1.1% (1/95)</td>
<td>2.2% (2/90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency/Week</th>
<th>Baseline</th>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>99</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Mean±SD (Median)</td>
<td>27.9±61.3 (7.0)</td>
<td>1.2±7.4 (0.0)</td>
<td>0.9±7.4 (0.0)</td>
</tr>
<tr>
<td>Range</td>
<td>0.0, 420.0</td>
<td>0.0, 70.0</td>
<td>0.0, 70.0</td>
</tr>
</tbody>
</table>

Heartburn Severity and Frequency

The symptoms of heartburn can vary in severity and frequency. The more severe the heartburn and the more frequent the symptoms, the more significant the impact on quality of life. At baseline, 89% (89/100) of subjects had moderate or severe heartburn and an average frequency of 79 times per week. This changed to 3.2% (3/95) of subjects and 2.3 times per week at 12 months and 5.5% at 24 months following LINX implantation. This observation strongly corroborates an improved quality of life following LINX treatment (see Table 18).

Table 18: Heartburn Severity and Frequency by Visit

<table>
<thead>
<tr>
<th>Severity</th>
<th>Baseline % (n/N)</th>
<th>Month 12 % (n/N)</th>
<th>Month 24 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0% (1/100)</td>
<td>57.9% (55/95)</td>
<td>51.1% (46/90)</td>
</tr>
<tr>
<td>Minimal – Occasional episodes</td>
<td>10.0% (10/100)</td>
<td>38.9% (37/95)</td>
<td>43.3% (39/90)</td>
</tr>
<tr>
<td>Moderate – Primary reason for visit</td>
<td>34.0% (34/100)</td>
<td>2.1% (2/95)</td>
<td>4.4% (4/90)</td>
</tr>
<tr>
<td>Severe – Interfering with activities of daily life</td>
<td>55.0% (55/100)</td>
<td>1.1% (1/95)</td>
<td>1.1% (1/90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from BL</th>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>93.7% (89/95)</td>
<td>91.1% (82/90)</td>
</tr>
<tr>
<td>Same</td>
<td>6.3% (6/95)</td>
<td>8.9% (8/90)</td>
</tr>
<tr>
<td>Worsened</td>
<td>0.0% (0/95)</td>
<td>0.0% (0/90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency/Week</th>
<th>Baseline</th>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>97</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Mean±SD (Median)</td>
<td>78.6±141.5 (35.0)</td>
<td>2.3±8.5 (0.0)</td>
<td>2.0±6.3 (0.0)</td>
</tr>
<tr>
<td>Range</td>
<td>0.0, 700.0</td>
<td>0.0, 56.0</td>
<td>0.0, 42.0</td>
</tr>
</tbody>
</table>
6.12 Additional Safety Assessments

**Endoscopy**

Endoscopy provides direct visual examination of the inner esophagus and the area where the implant is located to determine if any mucosal damage occurred. A total of 97 subjects had an endoscopy at 12 months. No device erosions or abnormal strictures were reported. Table 19 displays findings from the 12 month endoscopy.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>% (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device erosion</td>
<td>0.0% (0/97)</td>
</tr>
<tr>
<td>Abnormal stricture</td>
<td>0.0% (0/97)</td>
</tr>
</tbody>
</table>

**Abdominal/Chest X-ray**

The abdominal/chest X-ray allows a radiographic examination of the implant site to evaluate the presence of the device and to evaluate if the device has migrated from the implant location by comparing the x-ray performed at implant discharge to the x-ray performed at 12 months. All devices were at the gastroesophageal junction and no device migrations were reported (Table 20).

<table>
<thead>
<tr>
<th>Assessment</th>
<th>% (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device at GEJ</td>
<td>100% (94/94)</td>
</tr>
<tr>
<td>No Device Migration</td>
<td>100% (93/93)</td>
</tr>
</tbody>
</table>

*Subject completed the discharge implant x-ray.

**Barium Esophagram**

The barium esophagram procedure was performed to ensure that swallowed contents move the length of the esophagus, through the implant site, and into the stomach. A total of 96 subjects had a barium esophagram at 12 months, of which normal swallow function was reported in 97% (93/96) of subjects (Table 21). For the three subjects not reporting normal swallow function at 12 months, the findings were not deemed to be clinically significant as the finding were not associated with dysphagia.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>% (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Swallow Function</td>
<td>96.9% (93/96)</td>
</tr>
</tbody>
</table>
**Manometry/Motility**

Manometry/motility testing is typically performed to characterize esophageal swallow and sphincter functions (LES length, LES resting tone, and peristaltic functions). Ninety-three subjects completed manometry/motility testing at the 12 month visit. Five subjects refused or did not show-up for scheduled manometry/motility tests, even when rescheduled. Results from manometry/motility testing are summarized in Table 22.

**Table 22: Summary of Manometry/Motility Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean±SD (Median)</td>
<td>Range</td>
<td>N</td>
<td>Mean±SD (Median)</td>
<td>Range</td>
</tr>
<tr>
<td>LES resting tone (mmHg)</td>
<td>99</td>
<td>17.5±12.5 (15.4)</td>
<td>0.0, 70.0</td>
<td>93</td>
<td>22.5±13.7 (19.5)</td>
<td>3.0, 115.9</td>
</tr>
<tr>
<td>LES overall length (cm)</td>
<td>96</td>
<td>3.4±1.3 (3.5)</td>
<td>0.9, 7.7</td>
<td>93</td>
<td>3.4±1.4 (3.1)</td>
<td>0.6, 6.3</td>
</tr>
<tr>
<td>LES abdominal length (cm)</td>
<td>95</td>
<td>1.6±1.3 (1.5)</td>
<td>-1.5, 5.0</td>
<td>92</td>
<td>1.7±1.1 (2.0)</td>
<td>-1.0, 4.1</td>
</tr>
<tr>
<td>% liquid swallows effective</td>
<td>99</td>
<td>93.6±9.6 (100.0)</td>
<td>70.0, 100.0</td>
<td>93</td>
<td>85.3±21.2 (100.0)</td>
<td>20.0, 100.0</td>
</tr>
<tr>
<td>LES residual pressure (mmHg)</td>
<td>94</td>
<td>3.8±4.5 (3.0)</td>
<td>-6.3, 22.2</td>
<td>93</td>
<td>7.3±6.6 (6.4)</td>
<td>-2.4, 24.8</td>
</tr>
<tr>
<td>% LES relaxation</td>
<td>50</td>
<td>82.8±19.6 (88.0)</td>
<td>18.0, 103.0</td>
<td>38</td>
<td>84.5±12.8 (90.0)</td>
<td>50.0, 100.0</td>
</tr>
<tr>
<td>Distal esophageal amplitude (mmHg)</td>
<td>100</td>
<td>78.1±27.4 (72.5)</td>
<td>35.0, 161.0</td>
<td>93</td>
<td>84.5±35.7 (81.3)</td>
<td>22.0, 192.1</td>
</tr>
</tbody>
</table>

**6.13 Side Effects**

**Ability to Vomit**

At 12 and 24 months, respectively, 98.9% and 93.3% of subjects reported the ability to vomit or no need to vomit and 1.1% reported the inability to vomit (Table 23).

**Table 23: Foregut - Ability to Vomit**

<table>
<thead>
<tr>
<th>Ability to Vomit</th>
<th>Baseline % (n/N)</th>
<th>Month 12 % (n/N)</th>
<th>Month 24 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/No need</td>
<td>95.0% (95/100)</td>
<td>98.9% (94/95)</td>
<td>93.3% (84/90)</td>
</tr>
<tr>
<td>No</td>
<td>0.0% (0/100)</td>
<td>0.0% (0/95)</td>
<td>1.1% (1/90)</td>
</tr>
<tr>
<td>No response</td>
<td>5.0% (5/100)</td>
<td>1.1% (1/95)</td>
<td>5.6% (5/90)</td>
</tr>
</tbody>
</table>
Belching

The inability to belch is a frequent complaint following antireflux surgery and was assessed by the Foregut questionnaire. At 24 months, 100% of subjects maintained the ability to belch. Clinical results for belching are reported in Table 24.

Table 24: Foregut – Ability to Belch

<table>
<thead>
<tr>
<th>Ability to Belch</th>
<th>Baseline % (n/N)</th>
<th>Month 12 % (n/N)</th>
<th>Month 24 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>100.0% (100/100)</td>
<td>98.9% (94/95)</td>
<td>100.0% (90/90)</td>
</tr>
<tr>
<td>No</td>
<td>0.0% (0/100)</td>
<td>1.1% (1/95)</td>
<td>0.0% (0/90)</td>
</tr>
<tr>
<td>No response</td>
<td>0.0% (0/100)</td>
<td>0.0% (0/95)</td>
<td>0.0% (0/90)</td>
</tr>
</tbody>
</table>

Bloating and Gas

Tables 25 and 26 report data for bloating and gas from the Foregut questionnaire. The majority of subjects at 12 and 24 months had the benefit of decreased frequency of bloating compared to baseline status. These findings are remarkable considering bloating and gas are typically common complaints following antireflux surgery.

Table 25: Foregut – Bloating Frequency

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Baseline % (n/N)</th>
<th>Month 12 % (n/N)</th>
<th>Month 24 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>21.0% (21/100)</td>
<td>60.0% (57/95)</td>
<td>61.1% (55/90)</td>
</tr>
<tr>
<td>Occasionally</td>
<td>39.0% (39/100)</td>
<td>34.7% (33/95)</td>
<td>32.2% (29/90)</td>
</tr>
<tr>
<td>Frequently</td>
<td>34.0% (34/100)</td>
<td>4.2% (4/95)</td>
<td>6.7% (6/90)</td>
</tr>
<tr>
<td>Continuously</td>
<td>6.0% (6/100)</td>
<td>1.1% (1/95)</td>
<td>0.0% (0/90)</td>
</tr>
<tr>
<td>No response</td>
<td>0.0% (0/100)</td>
<td>0.0% (0/95)</td>
<td>0.0% (0/90)</td>
</tr>
<tr>
<td>Change from BL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td></td>
<td>60.0% (57/95)</td>
<td>58.9% (53/90)</td>
</tr>
<tr>
<td>Same</td>
<td></td>
<td>34.7% (33/95)</td>
<td>31.1% (28/90)</td>
</tr>
<tr>
<td>Worsened</td>
<td></td>
<td>5.3% (5/95)</td>
<td>10.0% (9/90)</td>
</tr>
<tr>
<td>No response</td>
<td></td>
<td>0.0% (0/95)</td>
<td>0.0% (0/90)</td>
</tr>
</tbody>
</table>

Table 26: Foregut – Gas Frequency

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Baseline % (n/N)</th>
<th>Month 12 % (n/N)</th>
<th>Month 24 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>27.0% (27/100)</td>
<td>47.4% (45/95)</td>
<td>52.2% (47/90)</td>
</tr>
<tr>
<td>Occasionally</td>
<td>38.0% (38/100)</td>
<td>35.8% (34/95)</td>
<td>35.6% (32/90)</td>
</tr>
<tr>
<td>Frequently</td>
<td>31.0% (31/100)</td>
<td>15.8% (15/95)</td>
<td>11.1% (10/90)</td>
</tr>
<tr>
<td>Continuously</td>
<td>4.0% (4/100)</td>
<td>1.1% (1/95)</td>
<td>1.1% (1/90)</td>
</tr>
<tr>
<td>No response</td>
<td>0.0% (0/100)</td>
<td>0.0% (0/95)</td>
<td>0.0% (0/90)</td>
</tr>
<tr>
<td>Change from BL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td></td>
<td>46.3% (44/95)</td>
<td>54.4% (49/90)</td>
</tr>
<tr>
<td>Same</td>
<td></td>
<td>38.9% (37/95)</td>
<td>30.0% (27/90)</td>
</tr>
<tr>
<td>Worsened</td>
<td></td>
<td>14.7% (14/95)</td>
<td>15.6% (14/90)</td>
</tr>
<tr>
<td>No response</td>
<td></td>
<td>0.0% (0/95)</td>
<td>0.0% (0/90)</td>
</tr>
</tbody>
</table>
6.14 Satisfaction at Baseline, 12 Months, and 24 Months

Subject satisfaction with their current condition is a critical measure of a GERD patient’s response to a treatment. In the Pivotal subject population, 95% of subjects at baseline were dissatisfied with their current condition. At 12 and 24 months post LINX implantation, only 3% of subjects were dissatisfied with their present condition as assessed Off PPI therapy (see Table 27).

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

7.0 Clinical Risk/Benefit Discussion

At present, there are limited treatment options for patients with gastroesophageal reflux disease (GERD): PPI therapy or fundoplication surgery. Patients who have persistent symptoms, despite PPI therapy, are often reluctant to have fundoplication surgery. Most patients will only elect a surgical fundoplication when the severity of the disease reaches a level where the benefits of a surgical fundoplication will likely outweigh the side effects and risks. As a result, there is a “Therapy Gap” which leaves patients in a treatment predicament: either accept life-long PPI therapy with insufficient symptom relief or commit to a fundoplication with its attendant side effects. The LINX device has been evaluated in two IDE clinical investigations to specifically select and treat chronic GERD patients who fall into this treatment gap. The results have been compelling, with the majority of the study subjects achieving significant control of GERD-related symptoms, objective evidence of reduced esophageal acid exposure and freedom from PPI dependence. The LINX procedure has shown to have minimal risk and be free of operative complications or procedure failures at a wide range of medical centers. Most study subjects were able to go home the same day of surgery on an unrestricted diet.
The LINX outcomes are consistent with the objectives of an interventional treatment, as defined by the Society of American Gastrointestinal Endoscopic Surgeons (SAGES), those goals are:

- elimination of symptoms
- healing of esophagitis
- prevention of complications
- maintenance of remission

Definitive relief of GERD-related symptoms was achieved in both the Feasibility and Pivotal trials. Subjects in the Pivotal trial had a long history of chronic dependence on PPI therapy prior to study entry (mean duration 6.3 years). Despite this, the majority of subjects had heartburn severe enough to affect daily activities of life. Following the LINX procedure severe heartburn was reduced to 1% of subjects at 12 months, and remained at 1% at 24 months. Severe regurgitation, defined as constant with the presence of aspiration into the lungs, was reduced from 13% at baseline to 1% at 12 months, and remained at 1% at 24 months.

The SAGES objective to heal esophagitis was achieved with the LINX procedure without addition of PPIs. At 12 and 24 months after implantation, 88% and 89% of subjects respectively were free of esophagitis, compared to only 60% of subjects at baseline. More advanced esophagitis, defined as Grade B, was reduced from 18% at baseline to 1% at 12 months and to 3.4% at 24 months.

The SAGES objective to have minimal complications was carefully monitored in both LINX IDE trials. The LINX clinical experience has shown no operative or hospital stay complications have been observed with the LINX implantation procedure. Side effects from the LINX treatment have been minimal and less than what is expected from other surgical antireflux procedures. Bloating, common with antireflux surgery, was not an issue, and actually improved following the LINX procedure with 40% of subjects reporting frequent or continuous bloating at baseline, which improved to 5% and 7% at 12 and 24 months, respectively. The ability to vomit and belch, often lost following antireflux procedures, was preserved in 99% of the subjects following LINX implantation. Early dysphagia was observed, which is common with esophageal
surgery, and resolved in almost all subjects. There were no deaths, device migrations, device erosions or infections at the esophagus.

The final SAGES objective is to show maintenance of symptom remission. The benefits of safety and effectiveness of the LINX procedure seen at 12 month follow-up continued to be seen at 24 months in the Pivotal trial, and in the Feasibility trial these benefits are seen at 36 months. Importantly, continued relief of symptoms is corroborated by long-term reduction in acid exposure, demonstrated through objective pH testing.

The LINX Reflux Management System shows clear evidence of significant clinical benefits with minimal risk. The risks and rate of serious adverse events were as expected for current antireflux surgical procedures, and new risks were identified. The clinical benefits experienced by a large majority of subjects included a reduction in distal acid exposure time, improvement in GERD symptoms, and elimination of PPI dependence. In the targeted population, the LINX device offers GERD patients a needed treatment option which has shown the ability to control the disease and its associated symptoms without introducing additional or unknown risks. The body of scientific evidence reported in the PMA application establishes clearly that the benefits derived from the LINX device outweigh its risks, and that approval is warranted.
References


Appendices

Appendix A: Pivotal Clinical Study Serious Adverse Event Narratives

Appendix B: GERD Health Related Quality of Life Questionnaire

Appendix C: Foregut Questionnaire

Appendix D: Pivotal Clinical Study Protocol
Appendix A

Pivotal Clinical Study Serious Adverse Event Narratives
Narratives for Related Serious Adverse Events (SAEs)

A total of six subjects were reported to have had a serious adverse event related to the device and/or procedure. A summary of Serious Adverse Events is provided in the table below, followed by a narrative for each subject with a device and/or procedure related SAE.

### Serious Adverse Events Related to Device and/or Procedure

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>As reported by the investigator</th>
<th>As adjudicated by the CEC</th>
<th>Total as reported by investigator and by the CEC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (n)</td>
<td>Subjects % (n)</td>
<td>Events (n)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>3</td>
<td>3% (3)</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1% (1)</td>
<td>2</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>1% (1)</td>
<td>1</td>
</tr>
<tr>
<td>Pain¹</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
</tr>
</tbody>
</table>

¹Causality reported as unknown
²CEC adjudicated nausea AE as related whereas Investigator did not
³Investigator reported AE as related whereas CEC did not

**Subject**

**Implant Date: March 20, 2009**

**SAEs: Nausea and Vomiting**

This 40 year old female, had serious adverse events of nausea and dysphagia. Clinical history at baseline included: severe heartburn (interferes with activities of daily life 20 times per day), severe regurgitation (constant, presence of aspirations 10 times per day), frequent and prolonged nausea (14 times per day per Foregut Questionnaire), and chronic back pain requiring daily narcotics.

The LINX implant procedure was performed on March 20, 2009 and within two weeks the subject developed symptoms of worsened nausea coupled with dysphagia. The subject was hospitalized for management of these symptoms, including esophageal balloon dilation in the region of the Gastroesophageal Junction (GEJ). The symptoms improved as a result of the dilation; however, dysphagia and nausea persisted.

On April 20, 2009 (30 days post-implant), the subject opted to have the LINX device removed. The LINX device was safely removed using a laparoscopic approach. At the time of explant, the Investigator noted no evidence of hiatal hernia. The magnetic beads were removed from their moderate-to-well developed capsule. The dysphagia resolved following device removal and the nausea improved to baseline status. No further complications or sequelae were reported.
Subject
Implant Date: June 9, 2009
SAEs: Dysphagia and Odynophagia

This 46 year old male, had serious adverse events of dysphagia and odynophagia. Clinical history at baseline included: severe heartburn (interferes with activities of daily life 20 times per day), appendectomy, and knee surgery.

The LINX implant procedure was performed on June 9, 2009. Approximately one week after the implant procedure, the subject experienced dysphagia and pain in the area of the implant device with both liquid and solid food swallows. This occurred on an ongoing basis. On July 1, 2009, the subject reported small signs of improvement, was able to eat small portions of semi-solid food (rice, yogurt and noodles), but still reported Odynophagia. Due to remaining dysphagia symptoms, endoscopic balloon dilatations were performed on July 8 (18 mm balloon) and July 28 (30 mm balloon) 2009. The subject’s condition did not resolve as a result of these interventions.

On August 13, 2009 the subject reported dissatisfaction and a decision was made to remove the device. Laparoscopic device removal surgery was performed on September 10, 2009. No incidents were noted during the removal procedure. The subject was discharged from the hospital in stable condition on September 11 2009. In the beginning of November 2009 the subject reported the dysphasia symptoms had resolved, and he was able to eat normal food.

Subject
Implant Date: July 17, 2009
SAE: Dysphagia

This 72 year old female, had a serious adverse event of dysphagia. The clinical history at baseline included: severe heartburn (interferes with activities of daily life 7 times per day), hypertension, hypothyroidism, depression, cholelithiasis, biliary colic, stomach bacteria and intestinal strangulation.

The LINX implant procedure was performed on July 17, 2009. Beginning five (5) days after implantation of the LINX device, the subject reported symptoms of dysphagia. Esophageal dilation was performed 14 days post implant and did not resolve the symptoms. Barium esophagram showed retained food in the esophagus. Manometry/motility determined that the subject had a loss of esophageal motility.

The device was safely removed by a laparoscopic approach on post-implant day 21. Manometry/motility performed 12 days after the device removal showed a total recovery of esophageal motility. Symptoms of dysphagia fully resolved. The subject remained part of the study and completed the 12 month follow-up. Swallow function by manometry/motility and barium swallow were normal at 12 months.

Subject
Implant Date: July 6, 2009
SAE: Pain and Vomiting

This 65 year old female, had serious adverse events of pain and vomiting. Clinical history at baseline included severe heartburn (interferes with activities of daily life 1 time per day), severe chest pain (interferes with activities of daily life 1 times per week) partial
thyroidectomy, hypertension, osteoporosis, hypercholesterolemia, neurofibromatosis and depression.

**Pain**
On February 27, 2010, subject had symptoms of chest pain, nausea and indigestion. She went to the emergency room and was admitted for observation to rule out myocardial infarction due to her cardiac risk factors. Stress test and cardiac enzymes were negative. Subject was discharged from hospital on February 28, 2010. Subject did not report any further episodes of pain. Since a cardiac event was ruled out, and the pain was an isolated episode, the Investigator and CEC both considered the pain to be of unknown causality.

**Vomiting**
The vomiting began about 3 months after device implantation. Episodes were monthly and then progressed to occurring weekly by June 2010. Episodes started with nausea and 10-12 hours later progressed to vomiting only green bile without any blood or undigested food. The vomiting occurred in small amounts until the episodes subsided (about ¼ of a cup with each emesis fill about one cup). Tests were performed to identify the cause of vomiting. Barium esophagram, manometry/motility, CT scan and hepatobiliary/cholecystokinin ductal scan were all normal. Gastric emptying study showed abnormal gastric emptying study demonstrating unusually rapid gastric emptying with only 4% gastric retention at one hour post meal ingestion. No evidence was found for abnormally slow gastric emptying.

In June 2010, a diagnosis of H. Pylori was made and medication started. However, the intermittent vomiting continued and a decision to remove the LINX device was made. Prior to explant the subject completed the 12 month evaluations and was found to have normal esophageal pH and improvement in GERD symptoms.

The device was explanted on June 28, 2010. At last follow-up in July 2010, the subject reported continued vomiting on a weekly basis. No conclusive cause was identified for vomiting and the Investigator reported the cause of the AE as unknown. However, the CEC could not definitely rule out the possibility of the LINX device and/or implant procedure as a potential cause. It is known that damage to the vagus nerve can occur during esophageal surgery and may lead to gastric emptying disorders. Gastroparesis was ruled out in this subject by a gastric emptying test, but rapid gastric emptying was seen. Vomiting beyond the early post-operative period has not been seen in other subjects following LINX implant.

**Subject**
**Implant Date: July 17, 2009**
**SAE: Vomiting**

This 66 year old male, had a serious adverse event of vomiting. The clinical history at baseline included: moderate heartburn (primary reason for visit 5 times per day), severe regurgitation (constant, presence of aspirations 5 times per day), heart murmur, cholesterolemia and benign prostatic hypertrophy. The LINX implant procedure was performed on July 17, 2009. On post-operative day 2, the subject reported not being able to keep any foods or fluids down and was admitted to the hospital for nausea and vomiting on July 19, 2009 and was given intravenous hydration and potassium chloride supplements. During the hospitalization, the subject had an upper esophagram which
showed normal flow of barium contrast through the duodenum without any gastroparesis or evidence of obstruction. The LINX device was noted to be in the normal position. The subject was subsequently discharged the following day. The subject reported to the clinic for routine follow-up a couple of days later and no dysphagia and tolerating an oral regular diet.

Subject
Implant Date: July 17, 2009
SAE: Nausea

This 49 year old female had a serious adverse event of nausea. The clinical history at baseline included: severe heartburn (interferes with activities of daily life 50 times per day), severe regurgitation (constant, presence of aspirations 10 times per day), depression, osteoporosis, Raynaud's disease, rheumatoid arthritis and Sjogren's syndrome. The subject was asked to stop her non-steriodal anti-inflammatory preoperatively but failed to do so. A hematoma approximately 1.5 cm was noted on the superior gastric wall just below the gastric fat pad but was thought to be of no consequence. This was observed for a period of time with no growth and was not thought to have any chance of being obstructive. Subject went home the same day as the implant procedure. The following day she started feeling nauseated with episodes of substernal chest pain. A barium swallow was performed which showed normal peristaltic activity in the esophagus. There was no evidence of perforation, and there was no evidence of gastroesophageal reflux. She was treated with Phenergan and was instructed to continue on solid foods with adequate liquid intake. On July 17, 2009, she was not improved and was admitted to the hospital for observation and intravenous hydration. She was discharged on July 19, 2009 with the nausea resolved but still having episodic substernal chest pain which resolved July 27, 2010 with sublingual Levsin and low-dose sublingual nitroglycerin.
Appendix B

GERD Health Related Quality of Life Questionnaire
Gastroesophageal Reflux Disease—Health Related Quality of Life

A. INTERVAL

ASSESSMENT TO BE COMPLETED BY SUBJECT

1. Questionnaire completed by:  
   ☐ 1  Telephone  ☐ 2  Visit

2.  
   ☐ 1  On PPIs Baseline
   ☐ 2  Off PPIs Baseline Date Stopped ___/___/____ (Day-Month-Year)
   ☐ 3  3-month (must be off PPIs)
   ☐ 4  6-month (must be off PPIs)
   ☐ 5  12-month (must be off PPIs)
   ☐ 6  Other_________  ☐ (on PPIs)  ☐ (off PPIs)

B. GERD-HRQL

Please check the numeric assessment of your GERD symptoms using the scoring provided below. Check only one box for each question.

Scoring Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Symptoms noticeable but not bothersome</td>
</tr>
<tr>
<td>2</td>
<td>Symptoms noticeable and bothersome but not every day</td>
</tr>
<tr>
<td>3</td>
<td>Symptoms bothersome every day</td>
</tr>
<tr>
<td>4</td>
<td>Symptoms affect daily activities</td>
</tr>
<tr>
<td>5</td>
<td>Symptoms are incapacitating – unable to do activities</td>
</tr>
</tbody>
</table>

1. How bad is your heartburn?  ☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

2. Heartburn when lying down? ☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

3. Heartburn when standing up? ☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

4. Heartburn after meals?  ☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

5. Does heartburn change your diet? ☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

6. Does heartburn wake you from sleep? ☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

7. Do you have difficulty swallowing? ☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

8. Do you have bloating or gassy feelings? ☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

9. Do you have pain with swallowing? ☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

10. If you take medication, does this affect your daily life? ☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

GERD-HRQL Total

11. How satisfied are you with your present condition?
   ☐ Satisfied  ☐ Neutral  ☐ Dissatisfied

_______________________________________________
Signature                                                            Day            Month                 Year
Appendix C

Foregut Questionnaire
Date of Assessment: __ ___/__ ___/__ __ __ __
Day         Month         Year
Subject Number: 03- ___ ___ - ___ ___ __
Subject Initials: (f) _____ (m) _____ (l) ______

Foregut Symptoms Questionnaire

ASSESSMENT TO BE COMPLETED WITH PATIENT (must be off PPIs)

<table>
<thead>
<tr>
<th>Interval</th>
<th>1. Baseline/Screening</th>
<th>2. 6-month</th>
<th>3. Other __________</th>
</tr>
</thead>
</table>

1.   0 = No Symptoms
     1 = Heartburn
     2 = Difficulty Swallowing
     3 = Regurgitation
     4 = Chest pain

   5 = Pain at top of stomach
   6 = Cough
   7 = Nausea
   8 = Asthma
   9 = Other

a. 1st Problem: __________
b. 2nd Problem: __________
c. 3rd Problem: __________
   ___ years ___ months ___ years ___ months ___ years ___ months

A. GRADING OF SYMPTOMS:

2a. Heartburn:

   □ 1. None
   □ 2. Minimal – Occasional episodes
   □ 3. Moderate – Primary reason for visit
   □ 4. Severe – Interfering with activities of daily life

2b. Heartburn:

   □ 1. Day
   □ 2. Week
   □ 3. Month

2c. Heartburn correlates with:

   □ 1. Nothing
   □ 2. Candy
   □ 3. Carbonated beverages
   □ 4. Alcohol
   □ 5. Smoking
   □ 6. Coffee
   □ 7. Fatty foods
   □ 8. Spicy foods
   □ 9. Other __________

   (check all that apply)

3a. Chest Pain:

   □ 1. None
   □ 2. Minimal – Occasional episodes
   □ 3. Moderate – Predictable with position change, straining or lying down
   □ 4. Severe – Interfering with activities of daily life

3b. Chest Pain:

   □ 1. Day
   □ 2. Week
   □ 3. Month

4a. Regurgitation:

   □ 1. None
   □ 2. Mild – After straining and/or large meals
   □ 3. Moderate – Predictable with position change, straining or lying down
   □ 4. Severe – Constant regurgitation, presence of aspiration into lungs

4b. Regurgitation:

   □ 1. Day
   □ 2. Week
   □ 3. Month

4c. Quality:

   □ 1. None
   □ 2. Acid liquid
   □ 3. Food
   □ 4. Acid and bitter
   □ 5. Bitter liquid
   □ 6. Other
### Date of Assessment: __/__ __ __/____

#### Subject Number: 03-____-____-____

#### Subject Initials: (f)______ (m)______ (l)_____

#### 5. Lung Problems:
*(check all that apply)*
- [ ] 1. None
- [ ] 2. Recurrent cough
- [ ] 3. Nocturnal cough
- [ ] 4. Recurrent Pneumonitis
- [ ] 5. Asthma
- [ ] 6. Change of voice
- [ ] 7. Other

#### 6a. Difficulty Swallowing:
- [ ] 1. None
- [ ] 2. Occasionally with course foods, lasting for a few seconds
- [ ] 3. Requiring liquids for clearing
- [ ] 4. Severe – Semi-liquid diet, history of meat impaction
- [ ] 5. Liquids only

#### 6b. Difficulty Swallowing: [ ] Times a
- [ ] 1. Day
- [ ] 2. Week
- [ ] 3. Month

#### 6c. Location:
- [ ] 1. None
- [ ] 2. Pharyngeal (throat)
- [ ] 3. Esophageal (chest)

#### 7a. Pain with Swallowing:
- [ ] 1. No
- [ ] 2. Yes

#### 7b. Pain with Swallowing: [ ] Times a
- [ ] 1. Day
- [ ] 2. Week
- [ ] 3. Month

#### 8a. Pain:
- [ ] 1. None
- [ ] 2. Above the stomach
- [ ] 3. Upper Abdomen
- [ ] 4. Lower Abdomen
- [ ] 5. Diffuse

#### 8b. Pain: [ ] Times a
- [ ] 1. Day
- [ ] 2. Week
- [ ] 3. Month

#### 8c. If yes to pain, is it associated with:
- [ ] 1. Meals
- [ ] 2. Nighttime (lying down)
- [ ] 3. Other

#### 8d. Intensity of pain:
- [ ] 1. Minimal
- [ ] 2. Moderate
- [ ] 3. Severe
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<tr>
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<td><strong>9a. Nausea/Vomiting:</strong></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Occasional episodes of nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequent and prolonged nausea, no vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous nausea, frequent vomiting</td>
<td></td>
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<td><strong>9b. Nausea/Vomiting:</strong></td>
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<td></td>
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<td><strong>9c. Ability to Vomit:</strong></td>
<td></td>
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<tr>
<td></td>
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<tr>
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<td>No need to vomit</td>
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<td><strong>10b. Ability to belch</strong></td>
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<tr>
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<td><strong>12. Increased Gas/Rectum:</strong></td>
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<td><strong>13a. Bowel Movements:</strong></td>
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</tr>
<tr>
<td></td>
<td>Normal</td>
<td></td>
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<tr>
<td></td>
<td>Constipation</td>
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<tr>
<td></td>
<td>Diarrhea</td>
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<td></td>
<td>Alternation of 2 &amp; 3</td>
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<tr>
<td><strong>13b.</strong></td>
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<td>Month</td>
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LINX™ Reflux Management System

Clinical Study Protocol

Study ID: 1802

Sponsor: Torax Medical Inc.
4188 Lexington Ave. North
Shoreview, MN 55126

Date of Final Original Protocol: 16-April-2008
Update to follow-up schedules and clarification of inclusion/exclusion criteria, etc. 24-Jun-08
Update to 120 enrollment limit, add dysphagia to risks, eliminate medication log, add eCRFs 31-Jul-08
Update inclusion criteria number 1 from a minimum age of 19 years to "Age of Majority", clarify amount of time screening tests are acceptable: 17-Nov-08
Update inclusion criteria no. 6, PPI scores: 22-Jan-09
Update inclusion criteria 6 and 8, exclusion criteria 13 and 15, 13-Feb-09
Update number of sites and number of enrollments, clarify exclusion criteria 4 and 15, update anticipated adverse events list 12-May-09
Update to extend follow-up schedule to 60 months: 12-Jan-11

Confidential Information

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May not be used, divulged, published or otherwise disclosed without the consent of Torax Medical Inc.
APPROVAL OF FINAL PROTOCOL

Torax Medical Inc.
Amy Derosier
Director of Clinical Research

_________________________  ______________________  __________
Name (print)                  Signature                 Date
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**INVESTIGATIONAL PLAN SUMMARY**

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<th>Study Title:</th>
<th>LINX™ Reflux Management System Clinical Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study ID:</td>
<td>Doc. No. 1802</td>
</tr>
<tr>
<td>Study Device:</td>
<td>An implantable single-use LINX device intended to augment the competence of the Lower Esophageal Sphincter (LES) to reduce or eliminate gastric reflux. The device is supplied sterile and is placed through a laparoscopic port.</td>
</tr>
<tr>
<td>Study Purpose/Objective:</td>
<td>The purpose of the study is to evaluate the safety and effectiveness of the LINX device in the treatment of Gastroesophageal Reflux Disease (GERD).</td>
</tr>
<tr>
<td>Target Indication for Use:</td>
<td>The Torax LINX™ device 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 drug therapy.</td>
</tr>
<tr>
<td>Study Design:</td>
<td>The study is a prospective, multi-center, single arm clinical study that will be conducted in the United States and Europe.</td>
</tr>
<tr>
<td>Study Duration:</td>
<td>Approximately 6 years (includes time for enrollment and completion of 60 month follow-up).</td>
</tr>
<tr>
<td>Investigational Study Centers:</td>
<td>This clinical evaluation will be conducted at up to twenty (20) U.S. investigational Centers and additional European Centers. Investigators will be selected among surgeons with experience performing anti-reflux laparoscopic procedures.</td>
</tr>
<tr>
<td>Subject Population:</td>
<td>Subjects ages ≥ 18 or Age of Majority according to Law in states or countries where 18 is considered a minor and &lt; 75 years seeking intervention for GERD who meet the study inclusion / exclusion criteria are eligible for this study. The study subject limit will consist of approximately 100 subjects that may be implanted with the device. Subjects entering study will be at least partially responsive to medical therapy (proton pump inhibitors) for their GERD symptoms and have tested positive (abnormal) in esophageal pH testing.</td>
</tr>
</tbody>
</table>
INVESTIGATIONAL PLAN SUMMARY (continued)

<table>
<thead>
<tr>
<th>Study Endpoints:</th>
<th><strong>Primary safety endpoint:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The primary safety endpoint is the rate of occurrence for serious device and procedure related adverse events. The primary safety endpoint will be assessed by reporting all adverse events and by estimating the rate of serious device and procedure related adverse events through 12 months post implantation. Safety will also be evaluated by endoscopy to assess the mucosa and abdominal/chest X-ray evaluations to verify device location at 12 months post implantation.</td>
</tr>
</tbody>
</table>

| | **Primary effectiveness endpoints:** |
| | Reduction in total distal esophageal acid exposure time defined by esophageal pH testing. Testing will be performed with subjects off PPIs. The subject’s baseline pH acid exposure time will serve as the control and be compared to the subject’s pH acid exposure time 12 months post implantation. |

| | **Success criteria** – At least 60% of subjects will have normalized or improved by at least 50% in total distal acid exposure |

| | **Secondary effectiveness endpoints:** |
| | Subjects GERD-HRQL (Health Related Quality of Life) scores will be assessed off all GERD medications. The subject’s baseline GERD-HRQL score will serve as the control and be compared to the subject’s GERD-HRQL 12 months post implantation. |

| | **Success criteria** - At least 60% of subjects will have a 50% reduction in total GERD-HRQL scores |

| | Subject’s average daily dose of 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. |

| | **Success criteria** - At least 60% of subjects will reduce their average daily PPI dosage ≥50% |

<table>
<thead>
<tr>
<th>Additional Information</th>
<th>Procedural information will be recorded at time of subject discharge:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>• Procedural success rate</td>
</tr>
<tr>
<td></td>
<td>• Time of overall procedure</td>
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<td>• Length of hospital stay</td>
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<th>Torax Medical Inc.</th>
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<td>Shoreview, MN 55126</td>
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<td>Tel: (651) 361-8900</td>
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<td>Fax: (651)361-8910</td>
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| Study Management: | Torax Medical Inc. or Designate |
1.0 Introduction

1.1 Background – Gastroesophageal Reflux Disease (GERD)

Prevalence

It is well understood that Gastroesophageal Reflux Disease (GERD) is a very serious health condition. GERD, which primarily manifests as heartburn, regurgitation, or both, is a chronic disorder associated with substantial morbidity and potential malignancy. GERD has a major adverse impact on subject’s quality of life. In industrialized nations the disease has become increasingly common, with an estimated prevalence of 7% in the general population based on the presence of daily symptoms.¹

Further the condition often leads to more serious health consequences. When reflux occurs on a chronic basis, it may result in esophagitis (an inflamed lining of the esophagus), narrowing of the esophagus, difficulty in swallowing, chronic sore throat and cough. Of considerable concern is the development of a precancerous condition known as Barrett’s esophagus may develop. Barrett’s esophagus is a condition in which the normal mucosal lining is replaced by an abnormal lining called specialized intestinal metaplasia, a condition that occurs in about 10% of people who have chronic GERD.² Up to 0.5% of patients who have Barrett’s esophagus may develop into esophageal cancer or adenocarcinoma³.

Lagergren, et al, report that the risk of esophageal adenocarcinoma is almost eight times as high among persons in whom heartburn, regurgitation, or both occur at least once a week as opposed to persons without such symptoms⁴.

Despite having maximum acid suppression therapy through medications there are still significant voids in the treatment of this disease. As evidence, there was a 216% increase in hospitalizations from 1998 to 2005 with a GERD diagnosis and during this same period of time, the inpatient procedure volume of antireflux surgery has decreased by 27%\(^5\) indicating a patient/physician dissatisfaction with the surgical option. A reported 10-20% of patients are dissatisfied with drug therapy\(^6\). The American Cancer Society estimates that during 2008 approximately 16,470 new esophageal cancer cases will be diagnosed in the United States\(^5\) most coming from patients with Barrett’s esophagus.

### 1.2 Current Treatment Options Including Benefits and Limitations

The normal physiological barrier to GERD is the lower esophageal sphincter (LES) muscle. The LES provides to close the junction between the esophagus and the stomach keeping gastric contents from refluxing into the esophagus. A competent LES keeps the esophagus closed to gastric contents and opens only during swallowing to allow food to pass into the stomach or when belching to allow air out of the stomach. A defective LES is the result of a weak sphincter tone that is insufficient to keep the esophagus closed allowing gastric contents to reflux into the esophagus. The LES may be weak due to poor resting tone, insufficient length, or increased frequency of inappropriate transient relaxations. Given this, the ideal therapeutic approach should aim to restore the functionality of the LES.

GERD is currently treated in one of three ways; drug therapy, endoscopic intervention or surgical intervention. These treatments aim to limit the extent of distal esophageal acid exposure by either reducing the acidity of the refluxing fluids or mechanically modifying the defective LES (endoluminally or surgically).

Drug therapy, which is the most common treatment for GERD, is directed at symptom relief and short term healing of esophagitis. Drugs known as proton pump inhibitors (PPIs), such as Prevacid\(^\text{®}\) and Nexium\(^\text{®}\), reduce the acid production in the stomach, but do not affect the function of the LES or treat the defective muscle tone, thereby treating the symptoms and not the disease.

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These drugs are taken daily but may fail to control the symptoms in 10% to 20% of subjects\(^6\). Even when symptoms are controlled the esophagus can continue to experience pathological injury\(^7,8\).

Importantly, these drugs do not treat the failing LES or eliminate the episodes of reflux\(^9\). The subject remains vulnerable to the higher risks of progression of the disease and developing adenocarcinoma as well as continued exposure to non-acid reflux (NAR). Frazzoni, et al, reports GERD subjects who were rendered symptom free with PPIs, but the esophageal acid exposure was still abnormal in 44%\(^8\). Furthermore, Sontag, et al, describe the results of a PPI trial where at 1 year follow-up, 55% to 67% of subjects remained healed (no recurrence of erosive reflux esophagitis), but 62.5% to 73.7% of those who developed erosive esophagus on therapy remained asymptomatic\(^10\).

Endoscopic procedures have been introduced that attempt to create geometry or compliance changes to the LES by various mechanical techniques including staple plications, bulking implants and radiofrequency energy. These treatments are designed to change the geometry, shape and/or compliance of the LES in order to restore competency to the gastroesophageal junction thereby reducing distal acid exposure. None specifically add functional tone back to the LES barrier. Clinical evaluations have occurred over the past decade to determine the safety and effectiveness of these procedures as well as determine the appropriate patient population suitable for these treatments. The procedure is performed transorally in an anesthetized patient who has moderate GERD with limited or no hiatal hernia. Normalization of esophageal pH exposure, by these endoscopic procedures, has been observed in 23-63% of patients\(^11,12,13\) and HRQL improvements of 55-74%\(^14\). The use of PPI therapy has been reported to be reduced by ≥50% in 51-80% of the patients\(^14\).

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The clinical outcomes to date have varied widely indicating a strong dependence on investigator experience and the technique used. Currently the bulking agent (Enteryx – Boston Scientific) and radiofrequency technology (Stretta – Curon Medical) have been removed from the market and a second bulking agent (Gatekeeper - Medtronic) has been discontinued. Plication technology (Plicator - NDO surgical, Esophyx – Endogastric Solutions) remains active in market development. Most recent clinical data on the Esophyx device, which at this time is the only endoscopic technology commercially available, report ph normalization of 34%, GERD-HRQL improvement of 73%, and freedom from daily PPI use of 85%, all at 12 month follow up15.

Surgical intervention or anti-reflux surgery is typically reserved for the most severe GERD patients and is often associated with hiatal hernia repair. The most common anti-reflux surgery is the Nissen Fundoplication which has numerous variations and techniques. Over the years there have been failed attempts to standardize this surgical methodology. Generally in this procedure, the upper portion of the stomach or fundus is dissected and permanently wrapped around the LES region of the esophagus and sutured in place. The fundus is intended to buttress or support a weak LES. Variations include the length, tightness, and geometry of the fundus wrap. Additionally, the fundus wrap is difficult to control; if too much fundus or too tight a wrap is applied, dysphagia occurs and if too little fundus is used or if it is too loose, efficacy may be limited. After surgery, new symptoms occur in approximately 5 to 8% of subjects and may include dysphagia, gas, bloating, increased flatus, and difficulty with belching or vomiting6. Catarci, et al, report a recurrence of GERD in up to 10.5% of cases, dysphagia and bloating in up to 57.9% of cases; and re-operation as often as 7.7% of the time16.

The Nissen Fundoplication surgical procedure has a reported efficacy of 73-85% normalization of esophageal acid exposure17,18,19. It is recognized that this reported success rate tends to be derived primarily from specialized, experienced operators which account for only a portion of patient treatments as opposed to procedures performed in the community hospital setting where outcomes are much more variable.

15 Lipham J. Medical and Surgical Aspects of Esophageal & Foregut Disorders: Pathophysiology & Treatment Meeting, Hawaii; Oral Presentation with Handout, February 2008
The surgical outcome is highly dependent on surgeon’s experience and frequently results in new symptoms as outlined above\textsuperscript{20,21}. For these reasons the numbers of Nissen procedures has declined over the last 5 years and it is becoming a procedure primarily for patients with complicated anatomy such as large hiatal hernia and complex GERD. Additionally, the efficacy of the fundoplication may wane over time, with as much as 62\% of subjects requiring medications to control recurrent reflux symptoms 10 years after surgery\textsuperscript{22}.

1.3 Study Rationale

The scientific rationale for the design of the LINX device is based on the premise that subjects with an incompetent (weak) LES will remain susceptible to gastroesophageal reflux until the LES barrier function is restored. The LINX device is designed to augment the LES function and is placed, via a laparoscopic approach, on the external aspect of the esophagus in the region of the LES. The device is comprised of a series of titanium beads with magnetic cores that are linked together with independent titanium wires. As a series, the device forms an annular shape, reference Figure 1.

\textbf{Figure 1: Illustration of the Magnetic Esophageal Sphincter}

The magnetic attraction of the beads provides a force to augment the LES and to restore its barrier function. When swallowing a bolus, the magnetic force decreases allowing distention of the esophagus and passage of the food bolus.

\textsuperscript{20} Kahrilas P. Laparoscopic Antireflux Surgery: Silver Bullet or the Emperor’s New Clothes? Am J Gastroenterol 1999, 94:7. 1721-1723
The natural function of the LES is to provide a barrier to prevent gastric reflux exposure to the distal esophagus. The “gold standard” objective measure of the degree of the reflux is esophageal pH (acid) monitoring. In this respect, the range of efficacy for all current treatments (anti-reflux surgery, PPI therapy and endoscopic surgery) results in pH normalization of 23-85% of patients. Current data of existing endoscopic treatments which target primarily the same patient population as the LINX device provide pH normalization ranging from 23-63 and most recent data from the only commercially available technology (Esophyx – Endogastric Solutions) reports normalization of 34%. These endoluminal devices have similar procedural requirements of placing a permanent implant, and requiring anesthesia in an operating room setting. The primary effectiveness endpoint in the LINX device study, is defined as at least 60% of subjects will have normalized or improved by at least 50% in total distal acid exposure. Given the minimal risk of a laparoscopic procedure we feel this provides an appropriate level of clinical benefit to the subject population to demonstrate the effectiveness of the treatment when considering alternative therapies for GERD.

Patient symptom improvement (GERD-HRQL) and drug therapy usage will also be analyzed as a secondary measure of success. Based on previous clinical trials of other GERD therapies such as the Medtronic Gatekeeper, the Boston Scientific Enteryx device and the Endogastric Solutions Esophyx device, all implants, efficacy targets for the GERD-HRQL and the drug therapy usage were the following: The average daily proton-pump inhibitor (PPI) average daily dosage was targeted for at least a 50% reduction and GERD-HRQL score were targeted at least a 50% improvement in score. Targets for the secondary endpoints of the LINX study have been set at least 60% of the study population achieving ≥50% reduction in GERD-HRQL and PPI use. In terms of safety, all serious device and procedure related adverse events will be recorded and analyzed.

Torax Medical and our medical advisors believe these endpoints are appropriate and represent clear clinical benefits of restoring the LES barrier function by the relief of symptoms and reduction or elimination of drug therapy dependence for the defined patient population.
2.0 Investigational Device: LINX Device

The implantable single-use device is intended to augment the competence of the Lower Esophageal Sphincter (LES) thereby reduce or eliminate gastric reflux. The device consists of a series of titanium beads with magnetic cores that are linked together with independent titanium wires. Sutures attached to eyelets are secured to form an annular shape at the time of implant, reference Figure 2. The magnetic attraction force of the beads provides the strength to augment an incompetent LES under normal gastric pressure. The device is supplied sterile and is placed through a laparoscopic port with a minimum internal diameter of 10mm.

**Figure 2: Illustration of the Magnetic Esophageal Sphincter**

![Image of Magnetic Esophageal Sphincter]

The device can be manufactured to different lengths, based on the number of beads linked together, accommodating the varied esophageal diameters. For purposes of this study, the smallest configuration will have 10 beads, and the largest will have 18 beads. The implant is provided with sutures attached to each end. The attached sutures are used by the physician to secure the ends of the device to each other at the time of implant. The device is implanted on the external aspect of the esophagus in the region of the LES.

**Esophagus Sizing Tool**

A single use esophagus sizing tool is used at the time of the implant to guide the physician into choosing an appropriately sized device, reference Figure 3.

**Figure 3: Esophagus Sizing Tool**

![Image of Esophagus Sizing Tool]

To determine an appropriately sized device for the subject, the Esophagus Sizing Tool is placed on the external aspect of the esophagus in the region of the LES. With the esophagus sizing tool wrapped around the esophagus, the physician is able to select the appropri-
ate device size based on the colored bead which aligns with the white bead, reference Figure 4.

**Figure 4: Esophagus Sizing Tool around the esophagus to determine appropriate sized device.**

The Esophagus Sizing Tool is considered to be a surgical instrument, and will be supplied to the investigative site labeled NON-STERILE. The investigative facility will sterilize the Esophagus Sizing Tool following internal standard sterilization of surgical instruments procedures, and the guidance provided in the *Instructions For Use*.

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<tr>
<th>BEAD COLOR</th>
<th>ASSOCIATED DEVICE (BEAD LENGTH)</th>
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<tbody>
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<td>10-Bead</td>
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<td>Orange</td>
<td>11-Bead</td>
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<td>Yellow</td>
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<td>Blue</td>
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<td>3rd Bead Post-Purple</td>
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### 2.1. Target Indication for Use

The Torax LINC™ device 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 drug therapy.
## 3.0 Study Design and Protocol Overview

The study is a prospective, multi-center, single arm clinical study that will be conducted in the United States and Europe.

The study is intended to evaluate the safety and effectiveness of the LINX device and its ability to augment the barrier function of the LES in GERD patients. The study will be performed at up to 20 investigational centers in the US and additional sites in Europe with approximately 100 subjects being implanted with the device.

The **Screening/Baseline Visit** will determine the eligibility of subjects to receive treatment with the LINX device.

Subjects will be followed at 48 hours/discharge, 1 week, 3 months, 6 months, 12 months and then annually to 60 months post implantation. The subject will return to the clinic 6 months after surgery for a follow up visit and then again at 12, 24 months and 60 months, reference Figure 5. Additional follow-up via either telephone interview or office visit will be conducted at 1 week, 3 months, 36 months and 48 months post implantation to assess medication use, adverse events and quality of life information. The study follow-up is outlined in Figure 5 and the data collected during all visits are outlined in Figure 6.

### Figure 5: Schematic of study design

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  Screeninh (Baseline Procedures)
    ↓
  Enrollment
    ↓
  Implant
    ↓
  48 hour/Discharge
    ↓
  1 Week Follow-up
    ↓
  3 Month Follow-up
    ↓
  6 Month Follow-up
    ↓
12 Month Follow-up for endpoint assessments and then annually from 24 months to 60 months
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**Figure 6: Evaluation Schedule**

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<th>48 hour/Discharge</th>
<th>1 Week</th>
<th>3 months</th>
<th>6 months (Office Visit)</th>
<th>12 months (Office Visit)</th>
<th>24 months (Office Visit)</th>
<th>36 months</th>
<th>48 months (Office Visit)</th>
<th>60 months (Office Visit)</th>
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<td>PPI, H2, Antacid and other Medication Use</td>
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<td>Barium Esophagram (Fluoroscopy)</td>
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<td>Adverse Events</td>
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X = Required  
O = Optional
4.0 Study Purpose and Objectives

4.1 Study Purpose/Objective

The purpose of this study is to evaluate the safety and effectiveness of the LINX device in the treatment of Gastroesophageal Reflux Disease (GERD).

5.0 Safety and Effectiveness Measures

5.1 Safety Endpoint

**Primary Safety Endpoint:**
The primary safety endpoint is the rate of occurrence of serious device and procedure related adverse events. The primary safety endpoint will be assessed by reporting all adverse events and by estimating the rate of serious device and procedure related adverse events through 12 months post implantation. Safety will also be evaluated by endoscopy to assess the mucosa and abdominal/chest X-ray evaluations to verify device location at 12 months post implantation.

The primary safety objective is to estimate the rate of serious, device and procedure related adverse events with a sufficient level of precision, no formal tests of hypothesis will be conducted.

5.2 Effectiveness Endpoints

**Primary effectiveness endpoints:**
Reduction in total distal esophageal acid exposure time defined by esophageal pH testing. Testing will be performed with subjects off PPI’s. The subject’s baseline pH acid exposure score will serve as the control and be compared to the subject’s pH exposure score 12 months post implantation.

**Success criteria** - At least 60% of subjects will have normalized or improved by at least 50% in total distal acid exposure

**Secondary effectiveness endpoints:**
Subjects GERD-HRQL (Health Related Quality of Life) scores will be assessed off all GERD medications. The subject’s baseline GERD-HRQL score will serve as the control and be compared to the subject’s GERD-HRQL 12 months post implantation.

**Success criteria** - At least 60% of subjects will have a 50% reduction in total GERD-HRQL scores
Subject’s average daily dose of 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.

**Success criteria** - At least 60% of subjects will reduce their average daily PPI dosage by at least 50%

### 5.3 Additional Information

Procedural information will be recorded at time of subject discharge:
- Procedural success rate
- Time of overall procedure
- Length of hospital stay

### 6.0 Investigational Study Centers

Up to twenty (20) US and European investigational centers will be allowed to participate in this clinical study. Investigators will be selected according to appropriate experience performing laparoscopic anti-reflux procedures.

### 7.0 Study Population

The Investigator(s) will be responsible for recruiting individuals to enroll in this study. Only those individuals satisfying the inclusion and exclusion criteria presented below may participate. Any questions regarding subject suitability will be referred to Study Management for review.

#### 7.1 Inclusion Criteria

Subjects included in the study must meet all the following criteria:

1. Subject 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 > 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 for at least 7 days prior to testing.
6. Subjects with symptomatic improvement on PPI therapy demonstrated by a GERD-HRQL score of $\leq 10$ on PPI and $\geq 15$ off PPI, or subjects with a $\geq 6$ point improvement when comparing their on PPI and off PPI GERD-HRQL score

7. GERD symptoms, in absence of PPI therapy (minimum 7 days)

8. If the subject is of child bearing potential 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

7.2 Exclusion Criteria

Subjects will not be included in the study if any of the following criteria apply:

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 follow-up 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 able 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

7.3 Subject Study Eligibility Process
Subjects that are being considered for enrollment in this clinical study will be evaluated for eligibility with several pre-operative tests as listed below:

- Esophageal pH
- Manometry/Motility
- EGD Endoscopy
- Barium Esophagram (Fluoroscopy)

At many Investigative Study Centers these tests are performed as part of the normal work-up for a surgical candidate whether they are being considered for antireflux surgery or for participation in this trial.

There also will be study specific testing as prescribed above in Figure 6.0 Evaluation Schedule. These tests are listed below:

- Health History
- GERD-HRQL Questionnaire
- Foregut Symptom Questionnaire
- PPI, H2, Antacid and other Medication Use

While the standard of care for a pre-operative surgical candidate varies from one Investigational Study Center to another. Subjects will be consented before any study specific activities (tests/questionnaires) are administered.

All subjects will undergo the following two part informed consent process.
1) Informed consent for further evaluation to determine eligibility for subject participation in the trial.

2) Informed consent for subjects meeting the eligibility criteria (inclusion/exclusion) granting consent to undergo the surgical placement of the LINX device.

**Figure 7: Subject Informed Consent Process**

- **Standard of Care Normal Surgical Work-up**
  - **(Informed Consent Form I)**
  - **Enrolled**
  - **Non-Standard of Care Work-up (Study Specific Testing to Determine Eligibility)**
  - **Subject Meets all Inclusion/Exclusion Criteria**
    - **Yes**
    - **Surgical Consent form signed (Informed Consent Form II)**
    - **Yes**
      - **Implant Procedure**
        - **No**
          - **Procedural Failure**
            - **Patient is followed up for safety endpoint through 3 months**
        - **Yes**
          - **LINX Device Implanted**
            - **No**
            - **Subject Withdrawn From Study**
            - **Follow-up Subject in accordance with protocol**
8.0 Informed Consent

Prior to Institutional Review Board (IRB)/Ethics Committee (EC) submission, the Investigator will prepare an informed consent form in accordance with this study protocol and all regulatory requirements (e.g. where applicable, 21 CFR Part 50 and in accordance with the Declaration of Helsinki) using the sample informed consent forms provided. A copy of the final IRB/EC approved Informed Consent must be submitted to the Study Management Center prior to starting the study at that investigational center.

Prior to study enrollment, all subjects (or their legal guardian) must document their consent for study participation and authorization for use and disclosure of health information by signing the appropriate IRB/EC-approved Informed Consent Forms.

There will be a two-part consent process. All subjects will sign Informed Consent I prior to undergoing any testing that is being conducted to evaluate their eligibility for implantation of the LINX™ device. Any subject who signs Informed Consent I is considered enrolled even if they do not undergo implantation of the LINX™ device. If subjects do not meet the eligibility requirements for participation based on testing, and/or are excluded based on other criteria they will be considered screening failures and will not be allowed to participate further in the study. These subjects, will not be included in any study endpoint analyses. If subjects meet all eligibility requirements they will need to sign a second consent document (Informed Consent II) which allows the subject to undergo the surgical placement of the LINX device.

The subject will have the opportunity to ask questions of, and receive answers from, the personnel conducting the study.

The Investigator will notify the Study Management Center and the IRB/EC within five (5) working days if device use occurs without subject informed consent.

Prior to follow-up at 24 months post implantation, all subjects (or their legal guardian) must document their consent for continued study participation by signing the appropriate IRB/EC-approved Informed Consent Addendum Form.
9.0 Study Assessments and Data Management

9.1 Demographic and Baseline Assessments

The following information will be collected at baseline/screening visit:

- Date of Birth
- Gender
- Race
- Medical History
- Height
- Weight
- Quality of Life (GERD-HRQL) on PPIs
- Quality of Life (GERD-HRQL) off PPIs (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL with the exception of antacids, which may be taken up until the morning of the visit)
- Foregut Symptoms Questionnaire off PPIs (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit)
- PPI, H2RA, and antacid use
- Esophageal pH testing (If testing is performed within 6 months of implant, subject does not need to repeat test. Subjects shall discontinue any GERD medications for at least 7 days prior to pH testing, with the exception of antacids, which may be taken up until the morning of the visit)
- Hiatal hernia evaluation
- Endoscopy (If testing is performed within 6 months of implant, subject does not need to repeat test)
- Barium Esophagram (If testing is performed within 6 months of implant, subject does not need to repeat test)
- Manometry/Motility testing (If testing is performed within 6 months of implant, subject does not need to repeat test)

9.2 Safety

9.2.1 Safety Measurements: Endoscopy and X-ray

The subject will undergo endoscopy to determine the presence or absence of esophagitis, the length of any hiatal hernia, if present, and to determine if any mucosal damage has occurred. The subject will also have X-rays taken to determine if the device has moved (migrated) from the implant location.
The Los Angeles Classification esophagitis grading scale will be used:

**Los Angeles Classification**

Not present: No Breaks (erosions) in the esophageal mucosa (edema, erythema, or friability may be present.

Grade A: One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length.

Grade B: One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds

Grade C: Mucosal breaks those are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference

Grade 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”

### 9.2.2 Adverse Events

Subjects will be queried at each follow-up regarding adverse events.

The occurrence and device-relatedness of all adverse events will be documented each time the subject is seen; at the Implant/Procedure Visit, 48 hours/Discharge, 6 months, 12 months, 24 months, and 60 months. The subject will also be queried via telephone call or office visit at 1 week, 3 months, 36 months, and 48 months.

### 9.3 Effectiveness Measurements

#### 9.3.1 Esophageal pH

Subjects will undergo esophageal pH testing to determine total distal esophageal acid exposure time.

Normalization for total distal ambulatory esophageal pH testing is defined as:

- pH < 4 for ≤ 4.5% of the time

If longer pH evaluations are received the total distal acid exposure time will be recorded as a 24 hour average (e.g. 48 hour Bravo testing)

**Note:** The same equipment used at baseline should be used at subsequent follow-ups.
9.3.2 GERD–HRQL (Health Related Quality of Life) Scale Questionnaire

A GERD-HRQL Questionnaire will be completed at baseline and at specific follow up visits. (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview.)

**Note:** The GERD-HRQL Questionnaire is to be given prior to any invasive test procedure

The GERD-HRQL is a scale that asks subjects to rate their GERD symptoms on a scale from 0 to 5.

**Scoring Scale:**

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

The following questions are asked:

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?
11. How satisfied are you with your present condition? Satisfied Neutral Dissatisfied
9.3.3 GERD Medication Use
The subject will be asked to report all current GERD medication use at the time of consent and all medications used post implantation throughout all follow-ups. All medications, including those taken for GERD symptoms must be reported. This includes, but is not limited to PPIs, H2RAs and antacids.

9.3.4 Manometry/Motility
The subject will undergo manometry/motility to measure LES pressure, length, amplitude of peristaltic contractions, and % effective swallows.

9.3.5 Barium Esophagram
The subject will undergo a barium esophagram at baseline to identify any anatomic abnormalities like the presence of strictures, reducibility of a hiatal hernia, and to assess bolus transport.

9.3.6 Additional Data Analysis - Foregut Symptoms Questionnaire
A Foregut Symptoms Questionnaire will be completed at baseline and at specific follow up visits. (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview.

Note: The Foregut Symptoms Questionnaire is to be given prior to any invasive test procedure
The Foregut Symptoms Questionnaire (Attachment C) asks subjects to grade their possible GERD related symptoms numerically on various scales for each symptom. The following symptoms are graded:
- Heartburn
- Chest pain
- Regurgitation
- Lung problems
- Difficulty swallowing
- Pain with swallowing
- Pain
- Nausea/Vomiting
- Belching
- Bloating
- Increased Gas/Rectum
- Bowel Movements
9.4 Data Management

All study data will be documented on electronic case report forms, which will be provided by the Sponsor or designate. Source documentation must be maintained in each subject’s chart; subject completed questionnaires will be considered their own source document. The coordinator should note that the questionnaires were administered in the subjects chart.

eCRFs and additional subject/study data will be maintained in a secure, password-protected study database.

10.0 Study Procedures

10.1 Roles and Responsibilities

Each investigational center will identify appropriate personnel to perform all study tasks.

10.1.1 Investigator-(s)

- This clinician will have responsibility to treat all subjects.
- Document all adverse events that occur during the study.
- Be responsible for signing the CRFs.
- Be responsible for providing medical care to subjects during the study.
- Be required to document experience performing anti-reflux surgery
- Have responsibility for conducting the initial diagnosis and subject enrollment consideration.
- Provide baseline assessments of the subject’s GERD.
- Interview subjects about their GERD symptoms
- Be available for each subject follow-up visit.

10.1.2 Study Coordinator

In addition to the Investigator, a Study Coordinator will be identified at each investigational center to facilitate and manage the study.

10.2 Screening/Baseline Visit

Male or female subjects aged ≥Age of Majority according to State or Country Law to <75 years will be assessed as suitable candidates for this study against the screening inclusion
and exclusion criteria. A log will be kept of all subjects screened for the study but not entered in the study. The reason(s) for excluding these subjects will be recorded.

A signed, dated, informed consent will be obtained from all subjects before any study specific procedures are performed.

The following assessments will be performed at the Screening/Baseline Visit and recorded on the appropriate CRF in order to determine eligibility for entry into the study:

- Date of Birth
- Gender
- Race
- Medical History
- Height
- Weight
- Record health history, female subjects of child bearing age will be given a pregnancy test.
- Review inclusion/exclusion criteria.

All subject records with prerequisite tests should be available prior to implant.

The following assessments and procedures should be completed prior to the implant procedure:

- GERD-HRQL Questionnaire on PPIs
- GERD-HRQL Questionnaire off PPIs (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview.)
- Foregut Symptoms Questionnaire off PPIs (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview.)
- Record details of any prior (over past year) and current medication use.
- Esophageal pH (Subjects shall discontinue any GERD medications for at least 7 days prior to pH testing, with the exception of antacids, which may be taken up until the morning of the visit. A full report including pH tracings along with all six (6) De-Meester components and record what test equipment was used.)
DeMeester Components:

1) % overall time pH <4
2) % upright time pH <4
3) % supine time pH <4
4) Total number of reflux episodes
5) Number of reflux episodes > 5 minutes
6) Longest reflux episode

- Manometry/Motility (Full report documenting all channels and individual amplitudes including tracings)
- EGD Endoscopy (Full report including images of proximal and distal view of esophagogastric junction (EGJ) and, where available, a DVD/CD recording of the entire procedure.)
- Barium Esophagram (Fluoroscopy)-(Full report and, where available, a DVD/CD recording of the entire procedure)

NOTE: Subjects are to be off of the following medications prior to surgery as would be consistent with other surgical treatments for GERD including non-steroidal anti-inflammatory medication. The Investigator will decide if blood thinners should be stopped prior to surgery.

### 10.3 Implant

The Investigator will then perform the procedure implanting the LINX device laparoscopically.

The following assessments or procedures must be completed:

- The implant procedure should be recorded on either a DVD/CD
- Record time of overall procedure
- Record any adverse events that occur during the procedure
- EGD Endoscopy is an optional part of the implant procedure that may be used to assess the acute performance of the device by viewing the gastroesophageal junction and the appearance of the valve (Full report including images of proximal and distal view of gastroesophageal junction (GEJ) and, where available, a DVD/CD recording of the entire procedure.)
- An abdominal/chest X-Ray (two views-AP and lateral) will be taken to confirm implant location prior to discharge or no later than 7 days post implant (Hard film or an electronic version and radiologist report regarding device placement).
- Before the subject leaves the hospital, discharge information shall be recorded (length of stay, date of discharge, and drug regimen).
- The subject will be instructed to discontinue any GERD medication.
- The subject shall be reminded of MRI contraindication.

10.4 48 Hours/Discharge

The following additional assessment must be completed during this follow-up.
- The subject will be asked about adverse events.

10.5 1-Week Follow-up (7 days ± 2 days)

The following assessment must be completed during this follow-up and may be conducted by office visit or telephone:
- The subject will be asked about adverse events.

10.6 3-Month Follow-up (90 days ± 30 days)

**Note:** The GERD-HRQL and Foregut Symptoms Questionnaires are to be given prior to any invasive test procedure

The following activities or procedures must be completed during this follow-up:
- GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
- Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
- The subject will be asked about current medication use and dosage.
- The subject will be asked about adverse events.
10.7 6-Month Follow-up (180 days ± 45 days)

The following assessments must be completed during this follow-up and must be conducted by office visit:

- GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit)
- Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit)
- The subject will be asked about current medication use and dosage.
- The subject will be asked about adverse events.

10.8 12-Month Follow-Up (365 days ± 60 days)

The following activities or procedures must be completed during this follow-up:

- Health History
- GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
- Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
- The subject will be asked about current medication use and dosage.
- Esophageal pH (Subjects shall discontinue any GERD medications for at least 7 days prior to pH testing, with the exception of antacids, which may be taken up until the morning of the visit. A full report including pH tracings along with all six (6) DeMeester components as listed in Section 10.2 and record what test equipment was used)
- Manometry/Motility (Full report documenting all channels and individual amplitudes including tracings)
- EGD Endoscopy (Full report including images of proximal and distal view of gastroesophageal junction (GEJ) and, where available, a DVD/CD recording of the entire procedure)
• Barium esophagram (Full report and, where available, a DVD/CD recording of the entire procedure)
• An abdominal/chest X-Ray (two views-AP and lateral) will be taken to confirm implant location. (Hard film or an electronic version and radiologist report regarding device placement)
• The subject will be asked about adverse events.

10.9  24-Month Follow-up (730 days +60 days)

The following activities or procedures must be completed during this follow-up:

• GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
• Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
• The subject will be asked about current medication use and dosage.
• EGD Endoscopy (Full report including images of proximal and distal view of gastroesophageal junction (GEJ) and, where available, a DVD/CD recording of the entire procedure)
• An abdominal/chest X-Ray (two views-AP and lateral) will be taken to confirm implant location. (Hard film or an electronic version and radiologist report regarding device placement)
• The subject will be asked about adverse events

10.10  36-Month Follow-up (1,095 days + 60 days)

The following activities or procedures must be completed during this follow-up:

• GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
• Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
- The subject will be asked about current medication use and dosage.
- The subject will be asked about adverse events

**10.11 48-Month Follow-Up (1,460 days ±60 days)**

The following activities or procedures must be completed during this follow-up:

- GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
- Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
- The subject will be asked about current medication use and dosage.
- The subject will be asked about adverse events

**10.12 60-Month Follow-up (1,825 days ±60 days)**

The following activities or procedures must be completed during this follow-up:

- GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
- Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)
- The subject will be asked about current medication use and dosage.
- EGD Endoscopy (Full report including images of proximal and distal view of gastroesophageal junction (GEJ) and, where available, a DVD/CD recording of the entire procedure).
- An abdominal/chest X-Ray (two views-AP and lateral) will be taken to confirm implant location. (Hard film or an electronic version and radiologist report regarding device placement)
- The subject will be asked about adverse events
11.0 Subject Completion and Withdrawal

11.1 Subject Completion

On completion of the study (either by legitimate completion or withdrawal), the investigator will complete the Withdrawal/Completion CRF.

11.2 Subject Withdrawal

A subject may withdraw (or be withdrawn) from the study prematurely for the following reasons:

- Withdrawal of consent by subject
- Serious adverse event (Adverse Event CRF must be completed)
- Protocol deviation
- Lost to follow-up (In case of early withdrawal of a subject, at least three (3) documented attempts should be made to contact the subject and have them come into the clinic).
- Termination of study by the Sponsor
- Investigator believes it is in the best interest of the subject
- Other (must be specified)

The reason for termination will be recorded in the Withdrawal/Completion CRF.

11.3 Subject Screening

A log of all subjects screened for the study but not entered into the study will be maintained by each investigational center. The reason(s) for screening failure of these subjects will be recorded on this log.

Screen failures are those subjects who are not eligible to start treatment following the screening assessment due to failure to meet inclusion and/or exclusion criteria or failure to sign the second consent form (Informed Consent II).

11.4 Treated Subjects

Only those subjects receiving the device (“treated subjects”) will be considered evaluable subjects.

Information on all subjects screened for the study will be recorded. If the subject is not enrolled into the study the reason for exclusion will be documented on the screening log. If
the subject is enrolled in the study but the LINX device is not implanted, the reason will be
provided on the implant form. Each subject enrolled in the trial will receive an identification
number.

12.0 Adverse Events

12.1 Adverse Event Reporting

Starting at the time of implantation and proceeding throughout the duration of the follow-up
period, the Investigator will closely monitor each subject for the development of clinical
evidence of adverse events.

An adverse event (AE) is an undesirable/unusual experience that occurs to a subject during
the clinical study, whether or not considered device related, including, (but not limited to)
those events that result from device use as stipulated in the protocol, that appears or wors-
ens during the clinical study. All adverse events that occur during the course of the follow-
up period, whether observed by the Investigator or by the subject, and whether or not
thought to be device- or procedure-related, will be reported in detail on the appropriate CRF
and followed to a satisfactory resolution.

Abnormal assessments that are judged by the Investigator as clinically significant will be
recorded as AEs if they meet the definition of an AE. Clinically significant abnormal
assessments that are detected during the study or are present at baseline and significantly
worsen following the start of the study will be reported as AEs or SAEs. The Investigator
will exercise his or her medical and scientific judgment in deciding whether an abnormal
assessment is clinically significant.

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

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>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.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Discomfort intense enough to cause interference with usual activities.</td>
</tr>
<tr>
<td>Severe</td>
<td>Incapacitating with inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical evaluation and or treatment.</td>
</tr>
</tbody>
</table>
12.1.1 Relationship to Study Devices/Procedures

The Investigator will also evaluate the relationship to the study device and/or procedure according to the following definitions:

- **Unrelated:** AE is due to the underlying disease state or concomitant medication or therapy not related to the study-specific devices or procedures.

- **Related:** AE had a strong temporal relationship to the study-specific devices or procedures and another etiology is unlikely.

- **Unknown:** Relationship of the AE to the study-specific devices or procedures and alternative etiology is unknown.

12.2 Serious Adverse Events

Adverse events that are defined as “serious”, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning will serve as a guide for defining reporting obligations.

The Investigator must decide whether each event meets the definition of a Serious Adverse Event (SAE). For the purposes of this study, a SAE will be defined as any untoward medical occurrence, whether related to the study device or procedure or not, that meets one or more of the following criteria:

- **Results in death**
- **Is life-threatening**
  
  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- **Requires subject hospitalization > 24 hours**
- **Requires prolongation of an existing hospitalization**
- **Results in persistent or significant disability/incapacity**
- **Results in fetal distress, fetal death, or a congenital anomaly or birth defect**
- **Requires intervention to prevent permanent impairment or damage.**

All serious adverse events (whether or not considered study-specific device- or procedural-related) must be reported immediately (within 24 hours of discovery) to the Study Management Center.
12.3  Anticipated Adverse Events and Complications

Anticipated adverse events are those events that are reasonably expected to occur as a result of the subject’s disease state, surgery or use of the LINX device.

The following is a list of anticipated adverse events and reactions that may occur. These may include, but may not be limited to the following:

**Risks of general surgery and anaesthesia:**
- Adverse reaction to anaesthesia (headache, muscle pain, nausea)
- Anaphylaxis
- Cardiac arrest
- Death
- Diarrhea
- Fever
- Hypotension
- Hypoxemia
- Infection
- Myocardial infarction
- Nausea
- Odynophagia
- Pneumonia
- Pulmonary embolism
- Respiratory distress
- Thrombophlebitis
- Vomiting
Risks of LINX device implantation procedure and/or device:

- Achalasia
- Bleeding
- Death
- Device erosion
- Device explant/re-operation
- Device failure
- Device migration (device does not appear to be at implant site)
- Diarrhea
- Dysphagia
- Inability to belch or vomit
- 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
- Worsening of preoperative symptoms (including but not limited to dysphagia or heartburn)

12.4 Unanticipated Adverse Device Effects

Unanticipated adverse device effects (UADEs) include any serious adverse effects on the health or safety of a subject or any life-threatening problem or death caused by, or associated with, the study device that are not typically associated with the procedure or the investigational device. All unanticipated adverse device effects must be reported to the IRB/EC within 10 working days and to the Study Management Center within 24 hours after the Investigator first learns of the adverse device effect.
13.0 Statistical Analysis Plan

13.1 Sample Size Determination

Minimum sample size requirements are calculated based on the primary efficacy objective using StatXact 5.0 software under an exact, one-sided test for one binomial population. The following hypothesis will be tested

\[ H_0: \pi \leq 0.60 \]
\[ H_a: \pi > 0.60, \]

where \( \pi \) is the proportion of subjects meeting the success criterion of 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 are 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 will be 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%.\textsuperscript{23,24} This level of precision is sufficient to adequately assess the safety of the device and procedure.

13.2 Analysis Methods

Analyses will be conducted according to the principles of Intent-to-Treat and Treated subjects. Subgroup analyses will also be performed.

Study Population Group Definitions (See Section 7.3 Subject Study Eligibility Process)

Intent to Treat - All subjects that meet all of the eligibility criteria and sign the second consent form (Informed Consent II).

Treatment - All subjects that meet all of the eligibility criteria and sign the second consent form (Informed Consent II) and are implanted with the LINX device.

13.3 Descriptive and Demographic Analyses

Continuous demographic and baseline variables of interest will be summarized via standard descriptive statistics (e.g. mean, standard deviation, median, range). Categorical demographic and baseline variables will be summarized via frequency distributions.

Objective 1: Safety

Analysis: The proportion of subjects free from a serious, device or procedure related adverse event through 3 months will be calculated, along with the corresponding lower 95% confidence limit. In addition, the rate of each type of distinct adverse event will be summarized. Events will be summarized based upon seriousness, expectedness, and the relationship to both the device and the implant procedure. The primary safety analysis will be performed using the Treated study population. Additional analysis will be performed using the Intent to Treat study population.

Objective 2: Effectiveness

Analysis: The primary efficacy objective will be evaluated by calculating the proportion of subjects meeting the success criterion: pH normalization or at least 50% reduction in distal acid exposure. The lower 97.5% confidence limit of the success rate will be calculated, and if the lower bound is greater than 60%, the objective will have been met. All efficacy analyses, primary and secondary, will be performed using the Treated study population. Additional analyses will be performed using the Intent to Treat study population.

The following secondary objectives will be evaluated. Formal hypothesis tests will be conducted for each objective under a hierarchical closed test proce-
dure. Hypothesis testing on the secondary objectives is dependent on meeting the primary efficacy objectives. All effectiveness:

1. Subjects GERD-HRQL (Health Related Quality of Life) scores will be assessed off all GERD medications. The subject’s baseline GERD-HRQL score will serve as the control and be compared to the subject’s GERD-HRQL 12 months post implantation.

   **Success criteria** - At least 60% of subjects will have a 50% reduction in total GERD-HRQL scores.

2. Subject’s average daily dose of proton pump inhibitor (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 implantation.

   **Success criteria** - At least 60% of subjects will reduce their average daily proton pump inhibitor dosage by at least 50%

Additional, supportive analyses will be conducted, including summaries of all performance outcomes at each study time point.

### 13.4 Continuous Analysis of Safety Results

Adverse events will be monitored continuously throughout this clinical trial. The analysis will be comprised of summary statistics and confidence intervals, as well as narratives for each subject.

### 14.0 Risk Analysis

The LINX Reflux Management System is manufactured under the Design Control provisions of 21 CFR 820.30 and ISO 13485. It is packaged to meet applicable standards.

#### 14.1 Potential Risks

Complications associated with surgical procedures and device implants have been compiled from the scientific literature and were identified as anticipated adverse events. As with any investigational or approved device, a potential exists for the occurrence of unanticipated adverse events. Torax Medical has no evidence to suggest that the risk of complications associated with use of the LINX device is greater than the risks posed by other existing marketed products/procedures except for those potential risks which are unique to the LINX™ device. See Table 1.
### Table 1: Potential Risks Unique to LINX™ Device

<table>
<thead>
<tr>
<th>Risk</th>
<th>Potential Clinical Effect</th>
<th>Mitigation Measures</th>
<th>Options For Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device migration - up or down esophagus</td>
<td>Device not effective</td>
<td>Animal testing to evaluate device stability</td>
<td>• Remove device</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Remove device, convert to fundoplication</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Remove device, return to PPI therapy</td>
</tr>
<tr>
<td>Device erosion</td>
<td>• Device not effective</td>
<td>• Device designed to minimize potential erosion</td>
<td>• Remove device</td>
</tr>
<tr>
<td></td>
<td>• Could effect swallow function</td>
<td>• Animal testing to evaluate device stability.</td>
<td>• Remove device, convert to fundoplication</td>
</tr>
<tr>
<td></td>
<td>• Possible infection</td>
<td></td>
<td>• Remove device, return to PPI therapy</td>
</tr>
<tr>
<td>Device integrity compromised (link breaks)</td>
<td>• Device not effective</td>
<td>Life cycle testing</td>
<td>• Remove device</td>
</tr>
<tr>
<td></td>
<td>• Potentially not effective if failure early during healing cycle</td>
<td>Material choices</td>
<td>• Remove device, convert to fundoplication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manufacturing methods</td>
<td>• Remove device, return to PPI therapy</td>
</tr>
<tr>
<td>Device integrity compromised (hermetic seal failed)</td>
<td>Tissue response to non-biocompatible material (magnetic core)</td>
<td>100% hermetic seal test</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Material choices</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Manufacturing methods</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surface coat magnetic core with biocompatible material</td>
<td></td>
</tr>
<tr>
<td>Magnetic field interaction with electrical implant or metallic, abdominal implants</td>
<td>• Change pacing rate</td>
<td>Labeling (contraindicated for use in subjects with electrical implant or metallic, abdominal implants)</td>
<td>• Subject receives alternative therapy for GERD (fundoplication, PPIS, etc.)</td>
</tr>
<tr>
<td></td>
<td>• Suspend ICD therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic Response</td>
<td>Inflammation, infection, foreign body reaction</td>
<td>Material choices</td>
<td>• Remove device</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manufacturing methods</td>
<td>• Remove device, convert to fundoplication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biocompatibility testing</td>
<td>• Remove device, return to PPI therapy</td>
</tr>
<tr>
<td>Exposure to MRI</td>
<td>• Large image artifact</td>
<td>MRI testing to determine effects</td>
<td>• Remove device</td>
</tr>
<tr>
<td></td>
<td>• Potential direct force on esophagus (acute)</td>
<td>Labeling (MRI contraindicated for subjects with device)</td>
<td>• Remove device, convert to fundoplication</td>
</tr>
<tr>
<td></td>
<td>• Potential heating on surface of device</td>
<td>Implant card states MRI contraindication</td>
<td>• Remove device, return to PPI therapy</td>
</tr>
<tr>
<td></td>
<td>• Permanent changes to device (magnetic field strength)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The proposed study will monitor the subjects at implant, 48 hours/discharge, 1 week, 3 months, 6 months, and 12 months. Furthermore, any risks associated with participation in this clinical study will be minimized and the study will be managed in accordance with 21 CFR 812 Investigational Device Exemptions, 21 CFR 50 Protection of Human Subjects, and 21 CFR 56 Institutional Review Boards, and ICH E6 Good Clinical Practices or current revision. Internationally, ISO 14155-Clinical Investigation of Medical Devices for Human Subjects/Clinical Investigation of Medical Devices and the Declaration of Helsinki.

### 14.2 Potential Benefits

The potential benefit to subjects being implanted with the LINX device are: to restore the normal function of the LES; to reduce or eliminate GERD related symptoms; and to reduce or eliminate dependence on GERD medications.

### 14.3 Conclusion

The conduct of this study is not anticipated to pose new types of risks from those identified for similar products/procedures. To date, Torax has no evidence to suggest that the incidence of complications associated with use of its LINX device will be greater than the risks posed by other existing marketed products. Therefore, the potential benefits of the LINX device outweigh the potential risks.

In conclusion, the need for the data from such a study together with the potential benefit of receiving GERD treatment in a controlled setting balances the risk related to participation in this clinical study.

### 15.0 Protocol Modifications

Neither Torax Medical Inc., its designees (subcontractors or contract research organization), nor the study Investigators may modify this protocol without obtaining written concurrence of each other and the IRB/EC in accordance with the countries regulations (as applicable).

Any deviations from this protocol undertaken to protect the life or physical well-being of a subject in an emergency situation must be reported to the Study Management Center within 48 hours of occurrence and the respective IRB/EC as soon as possible, but in no event later than five (5) calendar days after the emergency occurs.
16.0 Study Materials

16.1 Packaging and Labeling

The LINX device labeling includes Part #, Lot #, Serial #, Use By Date and the statement: “CAUTION—Investigational Device. Limited by Federal (United States) Law To Investigational Use.” Serial numbers will be tracked to ensure traceability of the product.

Labeling describing all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions will be provided in the Instructions for Use supplied with the product. (Attachment B)

16.2 Handling and Storage

The Investigator must ensure that the devices are stored according to the Instructions For Use.

The products are not to be used after the use by date indicated on the label. If a package is damaged, sterility cannot be assured and the contents should not be used. Do not re-sterilize the product.

All supplies are to be used only for this protocol and not for any other purpose. The Investigator must not destroy any unused supply, and is to return all unused product to sponsor.

16.3 Product Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or the head of the medical institution (where applicable), or designated center staff (e.g., storage manager, where applicable) must maintain investigational product accountability records throughout the course of the study.

16.4 Product Implant Technique

LINX Device Implant Technique (See Attachment B - Instructions For Use)

17.0 Study Administration

This study will be conducted in English.
17.1 Institutional Review Board (IRB)/Ethics Committee (EC) Approval

This protocol, Consent Form, and Authorization for the Use and Disclosure of Health Information (as applicable) must be reviewed and approved by the respective IRB/EC and the Study Management Center before subject enrollment. Changes to the protocol must be approved in writing by the Study Management Center and the IRB/EC (as applicable) before the change is implemented.

Prior to subject enrollment, a signed copy of the IRB/EC approval letter addressed to the Investigator must be submitted to the Study Management Center, certifying trial approval. The letter should reference this protocol by title, date and number/revision number as well as the approved Consent Form and HIPAA Authorization (as applicable). Investigators are responsible for submitting and obtaining initial approval and continuing approval from the IRB/EC and forwarding copies of the approval letters to the Study Management Center. The original letters are to be kept in the investigational center Regulatory Document Binder designated for this study.

The Investigator will notify the Study Management Center within five (5) working days of withdrawal of IRB/EC approval.

17.2 Name, Address and Chairperson of each IRB

At the time of this submission no IRBs or ECs have approved the study.

17.3 Name and Address of all Investigators

At the time of this submission, no Investigators have signed an agreement to participate in the study.

17.4 Investigator Agreement and Financial Disclosure

Each Investigator will sign the Investigator’s Agreement before beginning the study, as required by countries’ regulations. The Investigator’s signature signifies his/her willingness to follow the protocol and all regulations and reporting requirements. In accordance with countries’ regulations, all investigators will also be required to sign a Financial Disclosure form, which certifies the Investigator’s and his/her immediate family’s financial interest in Torax Medical Inc. and study outcomes. Investigators must inform the Study Management Center of any changes to the information within the financial disclosure throughout the course of the study and for a period of two years after the device is approved by the FDA or the study is terminated, whichever is later.
17.5 Subject Confidentiality
All information and data sent to Torax Medical Inc. and/or its designees concerning subjects and their participation in this study are considered confidential by Torax Medical Inc. and its designees (subcontractors or contract research organization). Only authorized Torax Medical Inc. personnel or approved contracted agents of Torax Medical Inc. will have access to some portions of these confidential files and will act in accordance with applicable regulations as required by HIPAA (as applicable). The IRBs/ECs and FDA also have the right to inspect and copy all records pertinent to this study. All data used in the reporting of this study will eliminate identifiable references to the subjects.

17.6 Study Management Center

Monitors will be restricted to qualified individuals trained in the aforementioned procedures as well as study-related documents. Copies of monitor training records will be maintained at the Study Management Center.

17.6.1 Monitoring Visits
This study will be conducted and monitored in accordance with recognized Good Clinical Practices (e.g. ICH E6 or current revision), 21 CFR 812, 21 FR 50, 21 CFR 54, and 21 CFR 56. Study monitors will be assigned to each site and will be qualified on the basis of education, experience, and training. Study monitors may include Torax Medical personnel, contracted Clinical Research Organization (CRO) personnel, or contracted independent clinical research monitors.

17.6.2 Investigational Center Qualification
Investigational Center qualification visits or phone calls will be conducted by the Study Management Center prior to acceptance of the site into this study. The site qualification visit will be scheduled to include time with the Primary Investigator, co-Investigators, study coordinator, and other study personnel. Areas of discussion include a review of personnel training, Investigator qualifications, adequacy of potential subject pool, research experience,
this study’s specific requirements for procedures and equipment, and a review of staffing and equipment availability and appropriateness. A written report of the qualification visit will be drafted by Study Management. Resolution of any concerns and/or completion of any appropriate study activities identified during the pre-study visit will be documented and submitted to the Primary Investigator.

17.6.3 Site Training

Study-specific training of study personnel is the responsibility of the Study Management Center and the Investigator. Study training will occur before the first device use. To ensure investigational plan and regulatory compliance as well as accurate data collection, site training will include a detailed review of this Investigational Plan, CRF completion, monitoring logistics, and regulatory requirements.

Investigational site study training personnel will ensure that study personnel:

- Submit this Investigational Plan to its IRB/EC and where applicable, the Competent Authority for appropriate review and obtain written approval for the conduct of the study prior to enrolling any subject for this study.
- Maintain all study correspondence, this Investigational Plan, and all related and required records on file at their facility.
- Assume full responsibility for the study investigation at their individual medical practices, clinics, and medical facilities.

17.6.4 Training of Investigators:

Training for Investigators will include some or all of the following:

- Receive materials illustrating the use of the LINX device.
- Perform implantation of the LINX device in one or more animals.
- Observe implantation of the LINX device by another Investigator.
- Be proctored by qualified individuals (Physician or Torax personnel)

All training will be conducted and documented prior to subject enrollment.

17.6.5 Case Report Forms

17.6.5.1 Electronic Case Report Forms (eCRFs)

Standardization of data collection will be achieved through the use of electronic Case Report Forms (eCRFs), which will be completed for each subject.
On completion, eCRFs will be reviewed for accuracy and signed by the physician. Corrections of data on the eCRFs will be made via database. Source documentation must be maintained in each subject’s chart.

eCRFs and questionnaires will be completed for all subjects enrolled in the study. Sites will be requested to complete eCRFs in a timely manner. Any discrepancies will be resolved through data clarifications (queries) with the clinical center.

The Investigator must review, sign and date each eCRF; these responsibilities cannot be delegated to another person. The Investigators are responsible for the accuracy and completeness of all data on the eCRFs.

Completed eCRFs will be reviewed at the investigational site by monitors at regular intervals throughout the study. Information on the eCRFs will be compared to information originally recorded on source documents related to the study (i.e. professional notes, laboratory reports, study-specific worksheets, etc).

A final study closeout visit will be conducted at each investigational site.

**17.6.6 Investigator Responsibilities**

The Investigator is responsible for ensuring that the study is conducted according to the Investigator Agreement, the Investigational Plan, and all applicable federal regulations for investigational device exemption studies. Specific responsibilities are listed in the Investigator Agreement and this Investigational Plan.

Records and reports must remain on file at the investigational site for a minimum of two years after the later of either the completion/termination of the investigational study or the date the LINX device receives market approval for the indication being studied. They may be discarded only upon approval from Torax Medical. The Investigator must contact Torax Medical before destroying any records and reports pertaining to the study to ensure that they no longer need to be retained. In addition, Torax Medical must be contacted if the Investigator plans to leave the investigational site to ensure that arrangements for a new Investigator or records transfer are made prior to Investigator departure.

**Records**

Records to be maintained by the Investigator which should be located in the designated regulatory study binder include:

- Investigational plan and all amendments
- Signed Investigator Agreement(s)
- Signed Financial Disclosure form(s)
- IRB/EC approval letter, including consent
- IRB/EC membership list or Letter of Assurance
- All correspondence relating to the study between the site and Study Management
- CVs and professional licenses for all Investigators
- Site personnel signature and responsibility list
- Clinical monitor sign-in log
- Blank set of each version of CRFs
- Subject Screening/Enrollment log
- Deviation log
- Adverse Event log
- Investigational device inventory log including: date, quantity, serial numbers of all devices, identification of all subjects the device was implanted, and final disposition
- Reports (including annual reports and a final report from the investigator)

The following records must be maintained for each subject enrolled in the study:

- Signed Consent Form
- Completed eCRFs and DCFs
- Adverse event reports and any supporting documentation
- Protocol deviations
- Complete medical records, including procedure reports, lab reports, professional notes, etc.
- Records pertaining to subject death during the investigation (including death records, death certificate, and autopsy report, if performed)

Torax Medical Inc. reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study at any time.

**Reports**

Investigators are required as indicated in Table 2 to prepare and submit to the Study Management Center and IRB/EC complete, accurate, and timely reports on this investigation when necessary, according to 21 CFR 812.150, applicable National Laws, and any conditions imposed by the reviewing IRBs, ECs, and/or any other regulatory agencies. Types of reports to be submitted include reports pertaining to unanticipated adverse device effects, withdrawal of IRB/EC approval, and deviations from the investigational plan.
Table 2 - Reports

<table>
<thead>
<tr>
<th>Report</th>
<th>Submit to:</th>
<th>Description / Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal of IRB/EC Approval</td>
<td>Torax Medical or Designate</td>
<td>Within five (5) working days of withdrawal of approval.</td>
</tr>
<tr>
<td>Deviation from Investigational Plan</td>
<td>Torax Medical or Designate and IRB/EC</td>
<td>Deviations from the Investigational Plan to protect the life or physical well being of a subject in an emergency – submitted within 48 hours to Study Management and no later than five (5) working days after the event.</td>
</tr>
<tr>
<td>Unanticipated Adverse Device Effects</td>
<td>Torax Medical or Designate and IRB/EC</td>
<td>If an unforeseen complication is determined to be an unanticipated adverse device effect, then the Investigators must initially notify the trial monitor within 24 hours and a report must be submitted within ten (10) working days after the Investigator first learns of the effect.</td>
</tr>
<tr>
<td>Use of Device Without Informed Consent</td>
<td>Torax Medical or Designate and IRB/EC</td>
<td>Submitted within five (5) working days after the use occurs.</td>
</tr>
<tr>
<td>Device Related Subject Death</td>
<td>Torax Medical or Designate and IRB/EC</td>
<td>Submitted immediately following the event.</td>
</tr>
<tr>
<td>Submission of Case Report Forms</td>
<td>Torax Medical or Designate</td>
<td>Submitted immediately following the evaluation.</td>
</tr>
</tbody>
</table>

The Investigator is required to submit an annual report to his/her IRB/EC with a copy to the Study Management, and a final report upon completion or termination of this study. The final report must be submitted within 90 days of completion or study termination.

The final report must include:

- Device name
- Number of subjects screened, enrolled, implanted, withdrawn and completed
- Number of devices received, used and returned
- Summary of all adverse events (anticipated and unanticipated)
- Summary of all serious adverse events
- Summary of all protocol deviations
- Summary of results, outcomes, and conclusions
17.6.7 Investigational Site Termination

Torax Medical Inc. reserves the right to terminate an investigational site for any of the following reasons:

- Failure to secure subject informed consent or Authorization for the Use and Disclosure of Health Information prior to study enrollment
- Failure to report unanticipated adverse device effects within 24 hours of discovery (to the Study Management Center) and ten working days (to IRB/EC) of learning of the event
- Failure to report serious adverse events within 24 hours of discovery
- Repeated investigational plan violations
- Repeated failure to appropriately complete CRFs
- Failure to enroll an adequate number of subjects
- Loss of or unaccounted for investigational product inventory
- Administrative decision by the company

18.0 Abbreviations and Definitions

ABBREVIATIONS:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>eC RF</td>
<td>electronic Case Report Form</td>
</tr>
<tr>
<td>DCF</td>
<td>Data Clarification Form</td>
</tr>
<tr>
<td>DSAE</td>
<td>Device and procedure-related serious adverse event</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act of 1996</td>
</tr>
<tr>
<td>H2RA</td>
<td>Histamine type 2 receptor antagonist</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IRB/EC</td>
<td>Institutional Review Board/ Ethics Committee</td>
</tr>
<tr>
<td>LES</td>
<td>Lower esophageal sphincter</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>UADE</td>
<td>Unanticipated Adverse Device Effect</td>
</tr>
</tbody>
</table>

DEFINITIONS: None
## Document Change History

<table>
<thead>
<tr>
<th>Document Revision</th>
<th>DCO Number</th>
<th>Reason For Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>169</td>
<td>New Release</td>
</tr>
<tr>
<td>2</td>
<td>201</td>
<td>Update to follow-up schedules and clarification of inclusion/exclusion criteria, etc.</td>
</tr>
<tr>
<td>3</td>
<td>214</td>
<td>Update to include up to 120 enrollments, add dysphagia to section 13.2, update to eCRFs.</td>
</tr>
<tr>
<td>4</td>
<td>278</td>
<td>Update inclusion criteria number 1 from a minimum age of 19 years to “Age of Majority”, clarify amount of time screening tests are acceptable.</td>
</tr>
<tr>
<td>5</td>
<td>312</td>
<td>Update inclusion criteria number 6 from “Subjects with symptomatic improvement on PPI therapy demonstrated by an GERD-HRQL score of ≤ 10 on PPI and ≥ 15 off PPI” to “Subjects with symptomatic improvement on PPI therapy demonstrated by a GERD-HRQL score of ≥ 15 off PPI therapy and the GERD-HRQL score on PPI therapy must be less than the off PPI therapy score”</td>
</tr>
<tr>
<td>6</td>
<td>335</td>
<td>Update inclusion criteria 6 from “Subjects with symptomatic improvement on PPI therapy demonstrated by a GERD-HRQL score of ≥ 15 off PPI therapy and the GERD-HRQL score on PPI therapy must be less than the off PPI therapy score” to “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”, update inclusion criteria 8 to state pregnancy test must be before implant, update exclusion 13 and 15 to include “history of or known” disease states.</td>
</tr>
<tr>
<td>7</td>
<td>363</td>
<td>Update number of sites and number of enrollments, clarify exclusion criteria 4 and 15, update anticipated adverse events list</td>
</tr>
<tr>
<td>8</td>
<td>637</td>
<td>Increase follow up period.</td>
</tr>
</tbody>
</table>

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Investigational Plan, Doc. No. 1802 CONFIDENTIAL Torax Medical LINX Device
Rev. 8
LINX™ Reflux Management System – Appendix D Page 53 of 55
19.0 References


15. Lipham J. Medical and Surgical Aspects of Esophageal & Foregut Disorders: Pathophysiology & Treatment Meeting, Hawaii; Oral Presentation with Handout, February 2008


ATTACHMENT A: INFORMED CONSENT FORM

ATTACHMENT B: INSTRUCTIONS FOR USE

ATTACHMENT C: CASE REPORT FORMS
II – Proposed Instructions for Use
1. SYSTEM DESCRIPTION

The LINX™ Reflux Management System is intended for use in the treatment of symptoms associated with Gastroesophageal Reflux Disease (GERD). The LINX™ device is placed at the area of the Lower Esophageal Sphincter (LES) designed to augment a weak LES and minimize or eliminate GERD related symptoms.

The LINX™ Reflux Management System is comprised of the following components:

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

The LINX™ Reflux Management System Implant consists of a series of titanium beads with magnetic cores that are connected with independent titanium wires to form an annular shape. The attractive force of the magnetic beads is designed to provide additional strength to keep a weak LES closed (Figure 1). During swallowing, the magnetic beads slide away from each other on the independent titanium wire “links” to allow esophageal distention as the bolus passes by (Figure 2).

The implant device is offered in multiple sizes to accommodate variation in esophagus size. The sizes are denoted by the model number (e.g., LS12 = 12 Bead Implant). The LINX™ Reflux Management System Esophagus Sizing Tool, packaged separately, is utilized to associate the esophagus size to an appropriate LINX™ implant device. An illustration of a “12 Bead” size LINX™ implant is provided in Figures 1 and 2.

2. INDICATION 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 drug therapy.
3. CONTRAINDICATIONS

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

4. WARNINGS

4.1. The device is to be placed around the esophagus including the anterior and excluding the posterior vagus nerve bundle. The device should never be placed outside both vagus nerve bundles.

4.2. The LINX™ Implant is considered MR Unsafe. After implantation, the patient should not be exposed to an MRI environment. The MRI environment could interfere with the magnetic strength and the function of the device. A recommendation should be made to patients receiving the LINX™ device to register their implant with the MedicAlert Foundation (www.medicalert.org) or equivalent organization. In the event alternative diagnostic procedures can not be used and MRI is required, the LINX device can be safely removed utilizing a laparoscopic technique that does not compromise the option for traditional anti-reflux procedures.

4.3. The device should not be exposed to temperatures above 100°C (212°F) as this could adversely affect the magnets and the function of the device.

5. PRECAUTIONS

5.1. Implantation of the device should only be performed by physicians who have experience in laparoscopic anti-reflux procedures and have received product specific training.

5.2. The sterile package and device should be inspected prior to use. If sterility or performance of the device is suspect or compromised, it should not be used.

5.3. The device is intended for single use only. Do NOT re-sterilize the device. Functionality and sterility of the device can not be assured if re-used.

5.4. The device is magnetic and will be attracted to ferrous objects in the surgical field and other surgical instruments that are ferromagnetic.

6. CLINICAL STUDIES

The LINX System has been evaluated in two prospective, single-arm, multicenter clinical trials with a combined enrollment of 144 subjects.

The first study enrolled 44 subjects at four clinical sites (2 US and 2 OUS) as part of a feasibility IDE trial. Performance outcomes for symptom improvement, reduction of PPI dependence and esophageal acid reduction have been reported through three years (Table 1).

<table>
<thead>
<tr>
<th>Performance Outcomes¹</th>
<th>12 Months % (n/N)</th>
<th>24 Months % (n/N)</th>
<th>36 Months % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in GERD-HRQL scores by ≥50%</td>
<td>97.4% (38/39)</td>
<td>88.6% (31/35)</td>
<td>96.3% (26/27)</td>
</tr>
<tr>
<td>Reduction in PPI therapy by ≥50%</td>
<td>89.7% (35/39)</td>
<td>82.9% (29/35)</td>
<td>87.5% (28/32)</td>
</tr>
<tr>
<td>pH normalization or ≥50% reduction in distal acid exposure²</td>
<td>79.5% (31/39)</td>
<td>90.0% (18/20)</td>
<td>85.0% (17/20)</td>
</tr>
</tbody>
</table>

¹Compared to the subject’s baseline data and assessed while off proton pump inhibitors
²pH monitoring is not performed in US subjects beyond the 12-month follow-up.
A total of 24/44 (54.5%) subjects experienced adverse events that were anticipated and consistent with what is generally expected following antireflux surgery such as dysphagia, pain, nausea and vomiting. No intra-operative complications, deaths, life-threatening events, device erosions, device migrations or infections were reported. Two subjects had serious adverse events related to the device and procedure that included one device removal for dysphagia and one hospitalization for chest pain <30 days following the device implant procedure. Both events resolved without clinical sequelae.

The second study, a pivotal IDE trial, enrolled a total of 100 subjects at 14 clinical sites (13 US and 1 OUS). All 100 subjects were implanted with the LINX device during a laparoscopic procedure with a mean duration of 39 minutes. Half the subjects (50/100) were discharged the same day as surgery, and the other half (50/100) were discharged the next day. Long-term data is available at 12 and 24 months with follow-up.

At 12 months, 64% of subjects had pH normalization or a ≥50% reduction in distal esophageal acid exposure, and the mean total acid exposure (percent time pH<4) was reduced from 11.9% at baseline to 5.4%.

Elimination of daily PPIs was achieved in 90.8% and 92.3% of subjects at 12 and 24 months, respectively. The proportion of subjects achieving at least a 50% reduction in daily use of PPIs from baseline was 93.0% at 12 months and 95.6% at 24 months.

A validated questionnaire called the GERD-HRQL Questionnaire was one method used to assess improvement in GERD-related symptoms. The questionnaire consists of a total of 10 questions that include 6 heartburn questions, 2 swallowing questions, 1 bloating/gas question and one question about GERD medications. Each question is scored on a scale of 0 (no symptoms) to 5 (incapacitating). The best possible score is 0 and the worst score is 50. The mean total GERD-HRQL score at baseline was 26.6 assessed off PPIs and 12.0 assessed on PPIs. At 12 and 24 months, the mean GERD-HRQL scores assessed off PPIs improved to 3.8 and 4.3, respectively. The proportion of subjects achieving at least a 50% reduction compared to baseline score was 92% at 12 months and 93% at 24 months.

Side effects associated with antireflux surgery were very minimal after the LINX implant. Additionally, other GERD-related outcomes (regurgitation (esophagitis, extra-esophageal symptoms and satisfaction) showed long-term improvement (Table 2).

Table 2: Side Effects and Additional Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Baseline 1</th>
<th>12 Months 1</th>
<th>24 Months 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to Belch</td>
<td>0%</td>
<td>1.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Inability to Vomit</td>
<td>0%</td>
<td>0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Bloating Frequency – Frequently/Continuously</td>
<td>40.0%</td>
<td>5.3%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Regurgitation – Severe or Moderate</td>
<td>57.0%</td>
<td>2.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Regurgitation – Mean frequency/week</td>
<td>27.9</td>
<td>1.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>40.0%</td>
<td>12.3%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Absence of Extra-Esophageal Symptoms</td>
<td>49.0%</td>
<td>86.3%</td>
<td>87.8%</td>
</tr>
<tr>
<td>Patient Satisfied with Present Condition</td>
<td>Off PPI 0%</td>
<td>94.7%</td>
<td>90.0%</td>
</tr>
<tr>
<td>On PPI</td>
<td>13.0%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

1Assessments completed off PPI therapy, unless noted
A total of nine (9) serious device and/or procedure related adverse events occurred in six (6) subjects for a SAE rate of 6% (Table 3). No intra-operative complications, deaths, device erosions, device migrations, infections at the esophagus or complications resulting in permanent disability occurred. The device was safely removed without complications or clinical sequelae for adverse events of dysphagia (n=3) and vomiting (n=1). Interventions for other SAEs included re-hospitalization in the early post-operative period for nausea and/or vomiting (n=2) and hospitalization to evaluate complaints of chest pain about 6 months post-implant (n=1). Through 12 months post-implant, 162 events considered related or unknown causality were reported (Table 4). Of the related adverse events, dysphagia was the most frequently reported event (76 events in 68 subjects) followed by pain (21 events in 20 subjects). Dysphagia was generally mild and self-resolving by 6 months were mostly mild and as expected (Table 4). At 24 months, no serious device and/or procedure related adverse events occurred and four mild events were reported (pain, inability to vomit, odynophagia and increased gas).

Table 3: Related Serious Adverse Events at 12 Months and 24 Months

<table>
<thead>
<tr>
<th>SAE</th>
<th>Number of Events at 12M¹</th>
<th>Number of Events at 24M</th>
<th>% Subjects (Number of Subjects/Total)</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious device and/or procedure related adverse</td>
<td>9</td>
<td>0</td>
<td>6.0% (6/100)</td>
<td>2.2%, 12.6%</td>
</tr>
</tbody>
</table>

¹Includes one SAE with adjudicated relationship to device/procedure of Unknown

Table 4: Related or Unknown Adverse Events at 12 Months

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Related or Unknown</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>AEs (n)</td>
<td>Subj. % (n)</td>
<td>AEs (n)</td>
<td>Subj. % (n)</td>
</tr>
<tr>
<td>Total</td>
<td>162</td>
<td>76% (76)</td>
<td>108</td>
<td>65% (65)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>76</td>
<td>68% (68)</td>
<td>54</td>
<td>49% (49)</td>
</tr>
<tr>
<td>Pain</td>
<td>25</td>
<td>24% (24)</td>
<td>8</td>
<td>8% (8)</td>
</tr>
<tr>
<td>Stomach Bloating</td>
<td>15</td>
<td>14% (14)</td>
<td>13</td>
<td>12% (12)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>7% (7)</td>
<td>4</td>
<td>3% (3)</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>8</td>
<td>8% (8)</td>
<td>4</td>
<td>4% (4)</td>
</tr>
<tr>
<td>Other: HICCUPS</td>
<td>8</td>
<td>8% (8)</td>
<td>7</td>
<td>7% (7)</td>
</tr>
<tr>
<td>Inability to belch or vomit</td>
<td>6</td>
<td>6% (6)</td>
<td>5</td>
<td>5% (5)</td>
</tr>
<tr>
<td>Other: DECREASED APPETITE</td>
<td>4</td>
<td>4% (4)</td>
<td>4</td>
<td>4% (4)</td>
</tr>
<tr>
<td>Other: BELCHING</td>
<td>2</td>
<td>2% (2)</td>
<td>2</td>
<td>2% (2)</td>
</tr>
<tr>
<td>Other: FLATULENCE</td>
<td>2</td>
<td>2% (2)</td>
<td>2</td>
<td>2% (2)</td>
</tr>
<tr>
<td>Other: WEIGHT LOSS</td>
<td>2</td>
<td>2% (2)</td>
<td>2</td>
<td>2% (2)</td>
</tr>
<tr>
<td>Other: FOOD IMPACTION</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Other: GLOBUS SENSATION</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Other: IBS/DYSPEPSIA</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Other: REGURGITATION OF STICKY MUCUS</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
7. Additional Information

The safety and effectiveness of the LINX™ Reflux Management System has not been established for the following conditions:

- Scleroderma
- Suspected or confirmed esophageal or gastric cancer
- Prior esophageal or gastric surgery or endoscopic intervention
- Hiatal Hernia >3 cm
- Distal esophageal motility less than 35 mmHg peristaltic amplitude on wet swallows or <70% (propulsive) peristaltic sequences or a known motility disorder such as Achalasia, Nutcracker Esophagus, and Diffuse Esophageal Spasm or Hypertensive LES.
- Esophagitis Grade C or D (LA Classification)
- Barrett’s esophagus
- Symptoms of dysphagia more than once per week within the last 3 months.
- Esophageal stricture or gross esophageal anatomic abnormalities (Schatzki’s ring, obstructive lesions, etc.).
- Esophageal or gastric varices.
- Lactating, pregnant or plan to become pregnant.
- Morbid obesity (BMI >35).
- Other electrical implant or metallic, abdominal implants
- Age < 18

8. DIRECTIONS FOR USE

8.1. Surgical Access

8.1.1. Gain surgical access through a laparoscopic port to the esophagus at the region of the gastroesophageal junction.

8.1.2. Dissect the soft tissues away from the outside of the esophagus at the location of the gastroesophageal junction. Tissue should be removed to expose the outer muscle of the esophagus. Create a tunnel under the posterior vagus nerve through the peri-neural tissue. The anterior vagus nerve will be included within the implant. Care should be taken to avoid injuring the vagus nerve bundles.

8.2. Sizing of the Esophagus

8.2.1. Use the LINX™ Esophagus Sizing Tool to determine the LINX™ Implant size. The LINX™ implant sizes are denoted by the model number (e.g., LS12 = 12 Bead Implant).

8.2.2. Bring the LINX™ Esophagus Sizing Tool into the surgical field through a laparoscopic port of appropriate internal diameter.

8.2.3. Place the sizing tool around the esophagus in the dissected space around the exposed outer muscle and through the tunnel created under the posterior vagus nerve bundle.

8.2.4. Perform sizing per the appropriate sizing tool instructions for use.
8.3. Placement of the LINXTM Implant

8.3.1. Bring the chosen LINXTM implant into the surgical field through a laparoscopic port of minimum internal diameter of 10 mm.

8.3.2. Place the device around the esophagus in the same location that was measured, reference Figure 3.

8.3.3. Using the suture provided, secure the ends of the device with a hand tied knot or a Top-Knot® device such that the eyelets of the device are touching or overlapping. Complete this method of securement for each set of white and green sutures for a total of two secured knots. Once secured, trim sutures, reference Figure 4.

8.3.4. It is recommended to repair Hiatal hernias in conjunction with the LINXTM implant procedure.

Figure 3 – Implant at Area of LES
Figure 4 – Completed Implant

9. PACKAGING/STORAGE

The LINXTM device is provided sterile and designed to remain sterile unless the primary product pouch has been opened or damaged. Store in a cool, dry place. If opened and not used, discard device or return device to Torax Medical Inc. Do Not Resterilize.

10. LIMITED WARRANTY

(a) Torax warrants that the product shall be free from material defects in materials and/or workmanship, and shall perform substantially in accordance with the written specifications, through the earlier of (i) the expiration of the shelf-life as specified on the applicable product labeling or (ii) the date on which the products are used or implanted.

(b) This limited warranty does not extend to damage caused by (i) abuse or misuse of any product, (ii) accident or neglect by you or a third party; (iii) use of the product other than in accordance with Torax's instructions or specifications; or (iv) any alterations made to the product after shipment.

(c) Torax's entire liability and your exclusive remedies under this limited warranty are, at Torax's option, for Torax to use commercially reasonable efforts to fix or replace the defective product.

(d) EXCEPT AS EXPRESSLY STATED ABOVE, TORAX MAKES NO WARRANTIES, EXPRESS OR IMPLIED, WRITTEN OR ORAL, BY OPERATION OF LAW OR OTHERWISE, OF ANY PRODUCTS OR SERVICES FURNISHED UNDER OR IN CONNECTION WITH THIS AGREEMENT. TORAX DISCLAIMS ALL IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, AND THOSE WARRANTIES ARISING BY STATUTE OR OPERATION OF LAW, OR FROM A COURSE OF DEALING OR USAGE OR TRADE.
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<td>Lot Number</td>
</tr>
<tr>
<td>SN</td>
<td>Serial Number</td>
</tr>
<tr>
<td></td>
<td>Use Before Date</td>
</tr>
<tr>
<td></td>
<td>Caution, consult accompanying documents</td>
</tr>
<tr>
<td></td>
<td>Refer to instructions for use</td>
</tr>
<tr>
<td></td>
<td>Do not use if package is damaged</td>
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<tr>
<td></td>
<td>Single Use Only</td>
</tr>
<tr>
<td>STERILE R</td>
<td>Contents Sterile: irradiation</td>
</tr>
<tr>
<td></td>
<td>Manufacturer</td>
</tr>
<tr>
<td></td>
<td>The LINX device is MR Unsafe</td>
</tr>
<tr>
<td>Rx Only</td>
<td>Caution: Federal (USA) Law restricts this device to sale by or on the order of a physician.</td>
</tr>
</tbody>
</table>
ESOPHAGUS SIZING TOOL

INSTRUCTIONS FOR USE
1. SYSTEM DESCRIPTION

The LINX™ Reflux Management System Esophagus Sizing Tool is a surgical instrument that is used as an accessory to the LINX™ Reflux Management System (packaged separately).

The device consists of a series of titanium beads with magnetic cores that are connected on a continuous stainless steel cable so that it can form an annular shape. The beads of the device are color coded to correspond with the size range of the LINX™ Reflux Management System Implants. An illustration of the LINX™ Reflux Management System Esophagus Sizing Tool is provided in Figure 1.

![Illustration of Sizing Tool](image-url)

Figure 5 – Illustration of Sizing Tool

2. INTENDED USE/INDICATION FOR USE

The LINX™ Reflux Management System Esophagus Sizing Tool is an accessory to the LINX™ Reflux Management System (packaged separately). See the Instructions for Use provided with the LINX™ Reflux Management System for intended use/indication for use.

3. CONTRAINDICATIONS, WARNINGS, PRECAUTIONS

The LINX™ Reflux Management System Esophagus Sizing Tool is an accessory to the LINX™ Reflux Management System (packaged separately). See the Instructions for Use provided with the LINX™ Reflux Management System for Contraindications, Warnings, and Precautions. Note: Temperature restriction of 100° C does not apply to the sizing tool.

4. ADVERSE EVENTS, CLINICAL STUDY

The LINX™ Reflux Management System Esophagus Sizing Tool is an accessory to the LINX™ Reflux Management System (packaged separately). See the Instructions for Use provided with the LINX™ Reflux Management System for Adverse Events and Clinical Study information.

5. DIRECTIONS FOR USE

5.1. Clean and Sterilize Before Use

5.1.1. Every sizing tool must be cleaned and sterilized before it is used. The Esophagus Sizing Tool was developed for sterilization by autoclave.

5.2. Cleaning Before Use

5.2.1. Every sizing tool must be disinfected and thoroughly cleaned before use. Clean and inspect the sizing tool carefully. Sterilize the sizing tool before surgery. Clean the instrument as follows:

5.2.2. Do not use corrosive cleaning agents. Cleaning solutions and rinses at or near a neutral pH (7.0) are best.
5.2.3. Do not use abrasive cleaners.
5.2.4. Rinse thoroughly with tap water or equivalent (distilled water, etc.).
5.2.5. Only a soft brush should be used.
5.2.6. Rinse the sizing tool with tap water for two minutes while brushing with a soft bristled cleaning brush to remove most or all of the visible gross debris.
5.2.7. Place the sizing tool into an enzymatic bath for five (5) minutes following the enzymatic cleaner manufacturer’s directions. Scrub the sizing tool with a soft bristled cleaning brush to remove any remaining debris from the instrument.
5.2.8. Rinse the sizing tool for two minutes using tap water.
5.2.9. Visually inspect the sizing tool under normal lighting to verify cleanliness. Thoroughly dry the sizing tool carefully with compressed air, or allow the sizing tool to air dry.

5.3. Sterilization Before Use
5.3.1. Steam autoclave sterilization is recommended. Do not sterilize in hot air.
5.3.2. Standard gravity autoclave steam cycle 132°C - 135°C for 30 minutes.
5.3.3. Standard pre-vacuum autoclave steam cycle 132°C - 135°C for 4 minutes.
5.3.4. Other time and steam temperatures cycles may also be used. However, user must validate any deviation from the recommended time and temperature.

5.4. Inspection and Functional Check
5.4.1. It is very important to carefully examine each sizing tool for breaks, cracks, loose or faded color coding, corrosion, broken wires, or other malfunctions before use. DO NOT USE DAMAGED INSTRUMENTS. DO NOT REPLACE COLOR CODING.

5.5. Surgical Access
5.5.1. Gain surgical access through a laparoscopic port to the esophagus at the region of the gastroesophageal junction.
5.5.2. Dissect the soft tissues away from the outside of the esophagus at the location of the gastroesophageal junction. Tissue should be removed to expose the outer muscle of the esophagus. Create a tunnel under the posterior vagus nerve through the peri-neural tissue. The anterior vagus nerve will be included within the implant. Care should be taken to avoid injuring the vagus nerve bundles.

5.6. Sizing of the Esophagus
5.6.1. Use the LINXTM Esophagus Sizing Tool to determine the LINXTM Implant size. The LINXTM implant sizes are denoted by the model number (e.g., LS12 = 12 Bead Implant).
5.6.2. Bring the LINXTM Esophagus Sizing Tool into the surgical field through a laparoscopic port of a minimum internal diameter of 10 mm.
5.6.3. Place the sizing tool around the esophagus in the dissected space around the exposed outer muscle and through the tunnel created under the posterior vagus nerve bundle, reference Figure 2.
5.6.4. Hold opposite ends of the sizing tool and wrap the sizing tool into a circular shape around the esophagus, reference Figure 3.
5.6.5. There is a white bead near the end of the sizing tool. With the sizing tool wrapped around the esophagus, align the white bead with the remaining colored beads of the sizing tool, reference Figure 4.

5.6.6. Determine the color that aligns with the white bead and referring to the sizing chart in Table 1, select the appropriate device for implantation.

<table>
<thead>
<tr>
<th>Bead Color</th>
<th>Associated LINX™ Implant Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Bead Pre-Orange</td>
<td>10-Bead</td>
</tr>
<tr>
<td>Orange</td>
<td>11-Bead</td>
</tr>
<tr>
<td>Yellow</td>
<td>12-Bead</td>
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<tr>
<td>Green</td>
<td>13-Bead</td>
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<tr>
<td>Blue</td>
<td>14-Bead</td>
</tr>
<tr>
<td>Purple</td>
<td>15-Bead</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Bead Post-Purple</td>
<td>16-Bead</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Bead Post-Purple</td>
<td>17-Bead</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Bead Post-Purple</td>
<td>18-Bead</td>
</tr>
</tbody>
</table>

5.6.7. Should the white bead align between two colors, choose the device with the higher number of beads.

6. **PACKAGING/STORAGE**

The LINX™ Sizing Tool is provided non-sterile. Store in a cool, dry place. If opened and not used, discard device or return device to Torax Medical Inc.
7. **LIMITED WARRANTY**

(a) Torax warrants that the product shall be free from material defects in materials and/or workmanship, and shall perform substantially in accordance with the written specifications, through the earlier of (i) the expiration of the shelf-life as specified on the applicable product labeling or (ii) the date on which the products are used or implanted.

(b) This limited warranty does not extend to damage caused by (i) abuse or misuse of any product, (ii) accident or neglect by you or a third party; (iii) use of the product other than in accordance with Torax’s instructions or specifications; or (iv) any alterations made to the product after shipment.

(c) Torax’s entire liability and your exclusive remedies under this limited warranty are, at Torax’s option, for Torax to use commercially reasonable efforts to fix or replace the defective product.

(d) EXCEPT AS EXPRESSLY STATED ABOVE, TORAX MAKES NO WARRANTIES, EXPRESS OR IMPLIED, WRITTEN OR ORAL, BY OPERATION OF LAW OR OTHERWISE, OF ANY PRODUCTS OR SERVICES FURNISHED UNDER OR IN CONNECTION WITH THIS AGREEMENT. TORAX DISCLAIMS ALL IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, AND THOSE WARRANTIES ARISING BY STATUTE OR OPERATION OF LAW, OR FROM A COURSE OF DEALING OR USAGE OR TRADE.
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</tr>
</tbody>
</table>
III – Proposed Patient Labeling
Dear Patient,

Torax Medical is committed to your care. This brochure is a simple guide designed to help you understand what to expect after your procedure and assist you to achieve the best results with the LINX™ Reflux Management System.

You play an important role in the success of your therapy with the LINX™ System. Please read this information carefully and consult your physician with any questions or concerns you may have.
POST-OPERATIVE PATIENT CARE INSTRUCTIONS

- Return to a normal, healthy diet as soon as tolerated. The opening and closing of your Lower Esophageal Sphincter (LES) that takes place when you eat and drink is important to ensure the proper functioning of the LINX™ System.

- Avoid foods that may bring on reflux, including coffee, alcohol, chocolate, and fatty foods. If you experience reflux after eating or drinking a particular food or beverage, write it down and avoid these choices in the future.

- Avoid foods that may bring on heartburn, including citrus, carbonated drinks, peppermint, tomato products, and spicy or spicy foods. If you experience reflux after eating or drinking a particular food or beverage, write it down and avoid these choices in the future.

- You may experience some discomfort or difficulty when swallowing. This is known as dysphagia, and is not uncommon after implant of the LINX™ System. In most cases, difficulty swallowing can be managed by taking smaller bites and chewing food more thoroughly. Dysphagia generally resolves 3-6 weeks after implant is made, and resolves on its own.

- If you experience difficulty swallowing, follow these steps:
  1. Drink a few sips of water before taking your first bite of food and between bites as necessary.
  2. Take small bites of foods that easily pass down your esophagus and into your stomach.
  3. Chew your food well before swallowing.
  4. Begin by identifying foods that may make swallowing more difficult for you. Bread, pasta, rice, and nuts may be more likely to cause problems.

- Carry your LINX™ Implant Card as notification to care providers that you have received a LINX™ System. If you lose this card, please contact your surgeon’s office to receive a replacement card.

FREQUENTLY ASKED QUESTIONS

Q. WILL THE MAGNETS WEAR OUT?
No. The LINX™ System uses permanent magnets.

Q. IS THERE A RISK OF MY BODY REJECTING THE LINX™ SYSTEM?
The LINX™ System was designed to minimize the risk of rejection. All areas of the device that come in contact with the body are made of materials that are used frequently in medical devices and have proven to be very stable.

Q. WHEN CAN I START EATING NORMALLY AGAIN?
Patients are encouraged to return to a normal, healthy diet as soon as tolerated. (Please see the Post-Operative Patient Care Instructions for more information.)

Q. WHEN CAN I RETURN TO NORMAL PHYSICAL ACTIVITIES?
Generally, patients are able to return to non-continuous activity within a couple of days; however, as with any surgical procedure, you should consult your physician regarding post-operative care.

Q. CAN I GO THROUGH AIRPORT SECURITY?
The LINX™ System should not affect airport security; however, all patients will be provided an implant card to have available in the event an issue arises.

Q. CAN I HAVE AN MRI TEST AFTER RECEIVING THE LINX™ SYSTEM?
No. Magnetic Resonance Imaging (MRI) tests are prohibited if you have received a LINX™ System. All patients will be provided with an implant card that warns against exposure to an MRI environment. A recommendation should be made to patients receiving the LINX™ Reflux Management System to register their implant with the Medical Devices Foundation (www.medicaldevices.org) or equivalent organization.
IV – Proposed Summary of Safety and Effectiveness Data
SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implanted GERD Device
Device Trade Name: LINX™ Reflux Management System
Applicants Name and Address: Torax Medical, Inc.
4188 Lexington Avenue North
Shoreview, Minnesota 55126
PMA Number: P100049
Date of Panel Recommendation: TBD
Date of Notice of Approval to the Applicant: TBD
Expedited: Not Applicable

II. 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 drug therapy.

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

Please refer to the device labeling for the list of the warnings and precautions.

V. DEVICE DESCRIPTION

The LINX™ Reflux Management System is intended for use in the treatment of symptoms associated with Gastroesophageal Reflux Disease (GERD). The LINX™ device is placed at the area of the Lower Esophageal Sphincter (LES) and is designed to augment a weak LES and minimize or eliminate GERD related symptoms.

The LINX™ Reflux Management System is comprised of the following components:

- LINX™ Reflux Management System Implant
- LINX™ Reflux Management System Esophagus Sizing Tool (packaged separately)
The LINX™ Reflux Management System Implant consists of a series of titanium beads with magnetic cores that are connected with independent titanium wires to form an annular shape. The attractive force of the magnetic beads is designed to augment the LES (Figure 1). During swallowing, the magnetic beads may slide away from each other on the independent titanium wire “links” to allow esophageal distention as the bolus passes by (Figure 2).

The implant device is offered in multiple sizes to accommodate variation in esophagus size. The sizes are denoted by the model number (e.g., LS12 = 12 Bead Implant). The LINX™ Reflux Management System Esophagus Sizing Tool, packaged separately, is utilized to associate the esophagus size to an appropriate LINX™ implant device.

The sizing tool consists of a series of titanium beads with magnetic cores that are connected on a continuous stainless steel cable so that it can form an annular shape. The beads of the device are color coded to correspond with the size range of the LINX™ Reflux Management System Implants. An illustration of the LINX™ Reflux Management System Esophagus Sizing Tool is provided in Figure 3.
VI. ALTERNATIVE PRACTICES AND PROCEDURES

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 three broad categories:

- Antacids;
- H₂ Receptor Antagonists (H₂RA); and
- Proton Pump Inhibitors (PPIs)

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, bulking agents and plication devices have emerged to treat GERD.
VII. MARKETING HISTORY

The LINX™ obtained CE mark in 2008 and marketing of the LINX™ device in Europe began. The LINX™ has not been withdrawn from the market in any country for any reason related to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Following is a list of the potential adverse effects (e.g., complications) associated with the LINX™ device:

- Achalasia
- Bleeding
- Death
- Device erosion
- Device explant/re-operation
- Device failure
- Device migration (device does not appear to be at implant site)
- Diarrhea
- Dysphagia
- Inability to belch or vomit
- 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
- Worsening of preoperative symptoms (including but not limited to dysphagia or heartburn)
- Early satiety
- Esophageal spasms
- Food impaction
- Hiccups
- Increased belching
- Weight loss

Following is a list of adverse effects (e.g., complications) associated with general surgery and anesthesia:

- Adverse reaction to anesthesia (headache, muscle pain, nausea)
- Anaphylaxis
• Cardiac arrest
• Death
• Diarrhea
• Fever
• Hypotension
• Hypoxemia
• Infection
• Myocardial infarction
• Nausea
• Odynophagia
• Pneumonia
• Pulmonary embolism
• Respiratory distress
• Thrombophlebitis
• Vomiting

For specific adverse events that occurred in the clinical studies, please see Section X.

IX. SUMMARY OF PRECLINICAL STUDIES

A. LABORATORY STUDIES

IN VITRO TESTING

In vitro (bench) testing has been performed to ensure the safe and reliable performance of the LINX™ device. Testing including mechanical integrity and interference with other devices due to the static magnetic field present around the device. Table 1 summarizes tests and results for the LINX™ and Table 2 summarizes tests and results for the Esophagus Sizing Tool. Results indicate the LINX™ and the Esophagus Sizing Tool perform according to established specifications.

Table 1: In-Vitro Testing – LINX™ Device

<table>
<thead>
<tr>
<th>Component / Construction</th>
<th>Study/Test</th>
<th>Description</th>
<th>Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Assembly</td>
<td>Mechanical Tensile Strength</td>
<td>Test to verify tensile force required to break the device</td>
<td>Pass</td>
</tr>
<tr>
<td>Complete Assembly</td>
<td>Mechanical Tensile Strength: Final Config. w/ Suture Knots</td>
<td>Test to verify tensile force required to break the sutured knot device</td>
<td>Pass</td>
</tr>
<tr>
<td>Complete Assembly</td>
<td>Mechanical Tensile Strength: Final Config. w/ Top Knots</td>
<td>Test to verify tensile force required to break the knot created with LSI Solutions Top Knot device</td>
<td>Pass</td>
</tr>
<tr>
<td>Component / Construction</td>
<td>Study/Test</td>
<td>Description</td>
<td>Test Result</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Complete Assembly</td>
<td>Corrosion Test</td>
<td>To determine device susceptibility to corrosion.</td>
<td>Pass</td>
</tr>
<tr>
<td>Complete Assembly w/out</td>
<td>Surface Analysis ESCA</td>
<td>To determine device susceptibility to corrosion.</td>
<td>Pass</td>
</tr>
<tr>
<td>magnetic core</td>
<td>Electron Spectroscopy</td>
<td>For chemical analysis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ESCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Assembly</td>
<td>MRI effect on device</td>
<td>Force applied by 1.5 Tesla coil MRI scan.</td>
<td>Observation Only</td>
</tr>
<tr>
<td></td>
<td>Effect of 1.5 Tesla coil</td>
<td>Effect of 1.5 Tesla coil on device magnetic strength.</td>
<td>Observation Only</td>
</tr>
<tr>
<td>Complete Assembly</td>
<td>Life Cycle Testing</td>
<td>Life cycle testing. Test for cyclic wear on expanding and contracting device over the life of an implant.</td>
<td>Pass – 10 year simulated use</td>
</tr>
<tr>
<td>Complete Assembly</td>
<td>Magnetic Field Strength</td>
<td>Magnetic field strength vs distance testing.</td>
<td>Pass</td>
</tr>
<tr>
<td></td>
<td>Modeling BEA/FEA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: In-Vitro Testing – Esophagus Sizing Tool

<table>
<thead>
<tr>
<th>Component / Construction</th>
<th>Study/Test</th>
<th>Description</th>
<th>Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Assembly</td>
<td>Mechanical Tensile and</td>
<td>Test to verify tensile force required to break the device is greater than specification.</td>
<td>Pass</td>
</tr>
<tr>
<td></td>
<td>Compression Strength</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**STERILIZATION, PACKAGING AND SHELF-LIFE**

The LINX™ and Esophagus Sizing Tool are individually packaged in device trays and held in place with a snap in retainer. Each device/tray is then placed inside a nylon reinforced Linear Low Density Polyethylene (LLDPE) pouch. Torax’s LINX™ device and packaging are terminally sterilized by gamma irradiation and the Esophagus Sizing Tool is provided non-sterile to the user.

A 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”. The sterilization validation effort demonstrated a Sterility Assurance Level (SAL) of $10^{-6}$ for the LINX™ device is obtained.

Microbiological safety validations were performed on the Esophagus Sizing Tool to demonstrate the effectiveness of cleaning and sterilization procedures to be used by the user met the AAMI Technical Information Report (TIR) No. 12 titled “Designing, Testing, and Labeling Reusable Medical Devices for Preprocessing in Health Care Facilities: A Guide for Device Manufacturers”. The cleaning and sterilization validation effort demonstrated an appropriate log reduction of tag spores after cleaning and that exposure to half cycles of common health care facility sterilization procedures provide complete lethality.

A thorough packaging and shelf-life validation has been performed to ensure the safe and reliable delivery of the LINX™ device and the Esophagus Sizing Tool. Testing conducted included device and packaging integrity assessments, which were completed at baseline, accelerated aging to simulate a 2 year shelf life, and accelerated aging to simulate a 4 year shelf life. The results provide evidence which shows that LINX™ device, Esophagus Sizing Tool, packaging materials and configuration have a four year shelf life.

**BIOCOMPATIBILITY**

The LINX™ device and the Esophagus Sizing Tool were subjected to biocompatibility tests selected in accordance with the International Standards Organization (ISO) 10993-1, Biological Evaluation of Medical Devices, and FDA’s guidance, Blue Book Memorandum #G95-1. The biocompatibility tests were selected based on the nature and duration of body contact with the LINX™ (tissue/bone contacting permanent implant device-permanent, i.e. >30 days) and the Esophagus Sizing Tool (contacts breached or compromised tissue for a limited period, i.e., less than 24 hours). The biocompatibility studies were performed in compliance with Good Laboratory Practice (GLP) regulations, 21 CFR Part 58. The LINX™ device and Sizing Tool passed all biocompatibility tests, indicating that the materials and processes used to manufacture the devices are biocompatible and suitable for their intended use. Biocompatibility test results for the LINX™ device are summarized in Table 3, and for the Sizing Tool in Table 4.
Table 3: GLP Biocompatibility Testing for LINX™ device

<table>
<thead>
<tr>
<th>Test Performed (literature citation, standard reference)</th>
<th>Test Article</th>
<th>Extract(s)</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxicity ISO 10993-5</td>
<td>Entire Packaged, Sterilized Implant</td>
<td>E-MEM</td>
<td>Pass</td>
</tr>
<tr>
<td>Sensitization ISO 10993-10</td>
<td>Entire Packaged, Sterilized Implant</td>
<td>0.9% Normal Saline (NS) Polyethylene Glycol (PEG)</td>
<td>Pass</td>
</tr>
<tr>
<td>Irritation/ Intracutaneous Reactivity ISO 10993-10</td>
<td>Entire Packaged, Sterilized Implant</td>
<td>0.9% NS Cotton Seed Oil (CSO)</td>
<td>Pass</td>
</tr>
<tr>
<td>Systemic Toxicity: Systemic injection ISO 10993-11</td>
<td>Entire Packaged, Sterilized Implant</td>
<td>0.9% NS CSO</td>
<td>Pass</td>
</tr>
<tr>
<td>Subchronic Toxicity - Subchronic 14-day (repeat dose) toxicity ISO 10993-11</td>
<td>Entire Packaged, Sterilized Implant</td>
<td>0.9% NS</td>
<td>Pass</td>
</tr>
<tr>
<td>Genotoxicity: Gene mutation (Ames Assay) ISO 10993-3</td>
<td>Entire Packaged, Sterilized Implant</td>
<td>0.9% NS PEG</td>
<td>Pass</td>
</tr>
</tbody>
</table>

Table 4: GLP Biocompatibility Testing for the Esophagus Sizing Tool

<table>
<thead>
<tr>
<th>Test Performed (literature citation, standard reference)</th>
<th>Test Article</th>
<th>Extract(s)</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxicity ISO 10993-5</td>
<td>Entire Packaged, Sterilized Tool</td>
<td>E-MEM</td>
<td>Pass</td>
</tr>
<tr>
<td>Sensitization ISO 10993-10</td>
<td>Entire Packaged, Sterilized Tool</td>
<td>0.9% Normal Saline (NS) Polyethylene Glycol (PEG)</td>
<td>Pass</td>
</tr>
<tr>
<td>Irritation/ Intracutaneous Reactivity ISO 10993-10</td>
<td>Entire Packaged, Sterilized Tool</td>
<td>0.9% NS Cotton Seed Oil (CSO)</td>
<td>Pass</td>
</tr>
<tr>
<td>Systemic Toxicity: Acute Systemic Injection ISO 10993-11</td>
<td>Entire Packaged, Sterilized Tool</td>
<td>0.9% NS CSO</td>
<td>Pass</td>
</tr>
</tbody>
</table>

B. ANIMAL STUDIES

A chronic animal study was conducted to assess the safety and the design of the LINX™ Reflux Management System. The study was conducted in compliance with Good Laboratory Practice (GLP) per 21 CFR 58. In the GLP study, twenty-five (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 based on the time of sacrifice, which occurred at 42 (2 groups), 91, 182, and 365 days post-implant.

Successful balloon actuations were obtained for all twenty-five (25) animals at all study time points. At sacrifice, all animals had devices encapsulated in fibrous tissue and, when evaluated histologically, appeared stable. Healing appeared to be complete by 3 months and the internal esophagus was noted as unremarkable and the LINX™ device healed well into external esophagus. Gross necropsy examination showed normal organs with minimal to moderate adhesions near the implant. The results of the study indicate that the device is safe and it was shown to actuate as expected.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Two prospective, non-randomized clinical studies have been conducted in the United States and Europe under IDE G060172 to support the safety and effectiveness of the Torax LINX™ Reflux Management System. The first was a feasibility study, conducted at two (2) investigational centers in the United States and at two (2) investigational sites in Europe. A total of 44 subjects were implanted with the LINX™ device to evaluate the safety of the device and collect preliminary performance information regarding its ability to reduce the symptoms of GERD by reinforcing the function of the LES. The safety and performance observed in this study led to the initiation of the pivotal study.

The second was a pivotal, multi-center, single arm clinical study that was conducted in the United States and Europe where one hundred (100) subjects were implanted with the LINX device at fourteen (14) sites. The pivotal study evaluated the safety and effectiveness of the LINX™ Reflux Management System to augment the barrier function of the LES in the treatment of GERD for those subjects diagnosed with pathological GERD as defined by abnormal pH testing and who continue to have chronic GERD symptoms despite anti-reflux drug therapy. Summaries of these clinical trials are presented in the following sections.

A. FEASIBILITY STUDY

STUDY DESIGN

The feasibility study was an observational, prospective, non-randomized, open label study conducted at four (4) investigational centers. Forty-four (44) subjects with confirmed GERD and incomplete symptom response to daily proton pump inhibitors (PPIs), as assessed by esophageal pH monitoring and the validated GERD quality of life questionnaire (GERD-HRQL)
were implanted with the LINX™ device. In this single-arm study, subjects served as their own treatment control. The primary safety objective of the feasibility study was to evaluate the incidence of adverse events. The performance objectives of the study were to monitor the improvement of GERD symptoms and LES function at various time points up to 60 months post implant and to optimize the implant technique. GERD symptoms were assessed by subjective measurements using the GERD-HRQL, and PPI use. LES function was characterized by objective measurements including 24 hour pH profile, manometry/motility, and barium esophagram. Follow-ups occurred at discharge, 2 weeks, 3, 6, and 12 months, then annually through 5 years.

**SAFETY AND EFFECTIVENESS RESULTS**

A total of 24/44 (54.5%) subjects implanted with the LINX™ 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). Serious adverse events (SAEs) occurred in two (2) subjects. One subject had dysphagia, which resulted in device explant. Following explant, the dysphagia resolved with no sequelae. A second subject had chest pain, which resulted in hospitalization and the chest pain was resolved. To date, no device migrations or erosions have been reported. Subjects continue to be followed for adverse events and no unanticipated adverse device effects have been reported.

The performance objectives included esophageal pH, GERD-HRQL results, and PPI use following treatment with the LINX device. Normalization or at least a 50% reduction in total acid exposure time was achieved in 79.5% of subjects at 12 months and in 90.0% at 24 months. Additionally, esophageal acid exposure times (% time pH <4) are significantly reduced following LINX implantation and are very stable over time with a total acid exposure time of 11.9% at baseline and 3.1% and 2.3% at 12 and 24 months, respectively. The baseline mean GERD-HRQL score was 25.7, at 1-year post-implant it was reduced to 3.8 (39/44), 2.4 (28/44) at 2-years, and 0.5 (6/44) at 3-years. Additionally, the majority of subjects were satisfied with their condition at all follow-up visits compared to no subjects being satisfied at baseline. As of last follow up, most patients continue to be off daily PPI drugs or have reduced their PPI therapy by >50%.
B. PIVOTAL STUDY

**STUDY DESIGN**

The pivotal study was a prospective, multi-center, single-arm study with subjects serving as their own treatment control. The purpose of the study was to evaluate the safety and effectiveness of the LINX™ device in the treatment of GERD through augmentation of the barrier function of the LES in GERD patients. The study was conducted at 16 sites in the United States and Europe, 14 of which had subjects that met eligibility requirements and were implanted with the investigational device. Ninety-six (96) subjects were implanted in the United States and four (4) in Europe that had confirmed GERD and incomplete symptom response to daily proton pump inhibitors (PPIs), as assessed by esophageal pH monitoring and the validated GERD quality of life questionnaire (GERD-HRQL) administered on and off PPI therapy.

1. Clinical Inclusion and Exclusion Criteria

Enrollment into the Torax LINX™ study was limited to subjects who met the following inclusion criteria:

- 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.
- Subject is a suitable surgical candidate, i.e., is able to undergo general anesthesia and laparoscopic surgery.
- 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).
- Patient requires daily proton pump inhibitor or other anti-reflux drug therapy.
- 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 for at least 7 days prior to testing).
- 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.
- GERD symptoms, in absence of PPI therapy (minimum 7 days).
- If the subject is of child bearing potential 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.
- Subject is willing and able to cooperate with follow-up examinations.
• Subject has been informed of the study procedures and the treatment and has signed an informed consent form.

Subjects were not permitted to enroll in the Torax LINX™ study if they met any of the following exclusion criteria:

• The procedure is an emergency procedure
• Currently being treated with another investigational drug or investigational device
• 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
• Suspected or confirmed esophageal or gastric cancer
• Any size hiatal hernia > 3 cm as determined by endoscopy
• Distal esophageal motility (average of sensors 3 and 4) is less than 35 mmHg peristaltic amplitude on wet swallows or < 70% (propulsive) peristaltic sequences
• Esophagitis – Grade C or D (LA Classification)
• BMI > 35
• Symptoms of dysphagia more than once per week within the last 3 months
• Diagnosed with Scleroderma
• Diagnosed with an esophageal motility disorder such as but not limited to Achalasia, Nutcracker Esophagus, or Diffuse Esophageal Spasm or Hypertensive LES
• Subject has a history of or known esophageal stricture or gross esophageal anatomic abnormalities (Schatzki’s ring, obstructive lesions, etc.)
• Subject has esophageal or gastric varices
• Subject has Barrett’s esophagus
• Cannot understand trial requirements or is unable to comply with follow-up schedule
• Pregnant or nursing, or plans to become pregnant during the course of the study
• Medical illness (i.e., congestive heart failure) that may cause the subject to be non-compliant with or able to meet the protocol requirements or is associated with limited life expectancy (i.e., less than 3 years)
• Diagnosed psychiatric disorder (e.g., bipolar, schizophrenia, etc.), subjects that exhibit depression that are on appropriate medication(s) are allowable
• Suspected or known allergies to titanium, stainless steel, nickel or ferrous materials
• Subject has an electrical implant or metallic, abdominal implants
2. Follow-up Schedule

Prior to treatment, all subjects underwent a medical history and physical exam, esophagogastroduodenoscopy (EGD), barium esophagram, esophageal manometry, and 48-hour ambulatory pH study (following a 7 day PPI medication wash out period). Additionally, each subject completed the GERD-HRQL (on and off PPI medication) and Foregut Symptom questionnaires. Follow-up per protocol was performed at discharge, 1 week, 3 months, 6 months and 12 months. During the Study, the protocol was amended to extend follow-up to 5 years, with follow-up visits occurring annually. Assessments for the efficacy endpoints were performed at 12 months (±60 days) from implant date. Additional assessments for secondary efficacy endpoints were performed at 24 months (±60 days) from implant date. GERD-HRQL and pH testing occurred at appropriate follow-up visits after the subject had stopped taking any PPI medications for 7 days.

ACCOUNTABILITY OF THE PMA COHORT

Informed Consent I (ICI) was signed by 257 subjects. Screening failures occurred in 154 of these subjects. Informed Consent II was signed by 103 subjects. Of these subjects, a total of 100 were implanted with the LIX™ system. Three (3) subjects were not implanted, therefore the Intent to Treat Group and Treated Group consisted of 103 and 100 subjects, respectively.

STUDY POPULATION DEMOGRAPHICS AND BASELINE PARAMETERS

A summary of key baseline subject characteristics are provided in Table 7. Subjects entered the study with abnormal esophageal pH and an incomplete response to PPI therapy.
Table 7: Summary of Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=100</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>50.4±12.4</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
</tr>
<tr>
<td></td>
<td>53.0 (18.3, 74.7)</td>
</tr>
<tr>
<td>BMI</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>27.9±3.4</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
</tr>
<tr>
<td></td>
<td>27.9 (19.8, 34.7)</td>
</tr>
<tr>
<td>Gender % (n/N)</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>52.0% (52/100)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>48.0% (48/100)</td>
</tr>
<tr>
<td>PPI Use (years)</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>6.3±4.8</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
</tr>
<tr>
<td></td>
<td>4.8 (0.2, 20.0)</td>
</tr>
<tr>
<td>Daily PPI Use %</td>
<td>100%</td>
</tr>
<tr>
<td>GERD-HRQL Total Score</td>
<td>Off PPI</td>
</tr>
<tr>
<td></td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>26.6±6.6</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
</tr>
<tr>
<td></td>
<td>27.0 (11, 47)</td>
</tr>
<tr>
<td></td>
<td>%Satisfied</td>
</tr>
<tr>
<td></td>
<td>0.0% (0/100)</td>
</tr>
<tr>
<td></td>
<td>On PPI</td>
</tr>
<tr>
<td></td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>12.0±6.8</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
</tr>
<tr>
<td></td>
<td>11.0 (0, 28)</td>
</tr>
<tr>
<td>Total % pH Time &lt;4</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>11.6±4.7</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
</tr>
<tr>
<td></td>
<td>10.9 (4.8, 25.4)</td>
</tr>
<tr>
<td>Esophagitis (%)</td>
<td>Grade A or B</td>
</tr>
<tr>
<td></td>
<td>40% (40/100)</td>
</tr>
<tr>
<td>Hiatal Hernia Size (%)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>44.0% (44/100)</td>
</tr>
<tr>
<td></td>
<td>1 cm</td>
</tr>
<tr>
<td></td>
<td>18.0% (18/100)</td>
</tr>
<tr>
<td></td>
<td>2 cm</td>
</tr>
<tr>
<td></td>
<td>24.0% (24/100)</td>
</tr>
<tr>
<td></td>
<td>3 cm</td>
</tr>
<tr>
<td></td>
<td>14.0% (14/100)</td>
</tr>
<tr>
<td>Heartburn –Frequency/week</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>78.6±141.5</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
</tr>
<tr>
<td></td>
<td>35.0 (0, 700)</td>
</tr>
<tr>
<td>Regurgitation – Frequency/week</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>27.9±61.3</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
</tr>
<tr>
<td></td>
<td>7.0 (0, 420)</td>
</tr>
</tbody>
</table>

SAFETY AND EFFECTIVENESS ENDPOINTS AND RESULTS

1. Safety Endpoint and Results

A total of nine (9) serious device and/or procedure related adverse events occurred in six (6) subjects. The upper 95% confidence limit on the estimate rate of serious, device and/or procedure related adverse events was 12.6% (Table 8). In three (3) subjects, an adverse event of dysphagia was serious as it resulted in the explant of the LINX™ device. Following explant, the dysphagia resolved with no sequelae in all cases. Two (2) subjects were briefly hospitalized in the early post-operative period due to nausea or vomiting, which resolved without further
Another subject was hospitalized twice during the course of the study, once for pain of unknown etiology and another time for explant of the device related to vomiting of unclear causality, but possibly related per CEC adjudication. Related SAEs as reported by Investigators and adjudicated by the CEC are displayed in Table 9. No deaths occurred during the study and no Unanticipated Adverse Device Effects were reported.

**Table 8: Primary Safety Endpoint**

<table>
<thead>
<tr>
<th>Primary Safety Endpoint</th>
<th>Number of Events</th>
<th>% Subjects (Number of Subjects/Total)</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious device and/or procedure related adverse event as reported by the investigator or CEC</td>
<td>9</td>
<td>6.0% (6/100)</td>
<td>2.2%, 12.6%</td>
</tr>
</tbody>
</table>

*Includes one SAE with adjudicated relationship to device/procedure of Unknown*

**Table 9: Serious Adverse Events Related to Device and/or Procedure**

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>As reported by the investigator</th>
<th>As adjudicated by the CEC</th>
<th>Total as reported by investigator and by the CEC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (n)</td>
<td>Subjects % (n)</td>
<td>Events (n)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>3</td>
<td>3% (3)</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1% (1)</td>
<td>2</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>1% (1)</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>1% (1)</td>
<td>1</td>
</tr>
</tbody>
</table>

*1Causality reported as unknown
2CEC adjudicated nausea AE as related whereas Investigator did not
3Investigator reported AE as related whereas CEC did not

Through 12 months, there were a total of 310 events in 88 subjects. Of these, 162 events were considered related or unknown causality (Table 10). Of the related adverse events, dysphagia was the most frequently reported event (76 events in 68 subjects) followed by pain (21 events in 20 subjects). Both dysphagia and pain are anticipated following anti-reflux surgery. Dysphagia was reported as mild in 71% (54/76) of events, defined as: an awareness of symptoms, but easily tolerated and minor irritant type causing no loss of time from normal activities.
Table 10: Any Related or Unknown to Device/Procedure

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

A total of 43 new adverse events were reported between the 12 and 24 month follow-up visits. Of these adverse events, 3 events were device and/or procedure related, 1 event was unknown causality, and 39 events were not related to the device or procedure. Table 11 summarizes the related or unknown adverse events that are new since the 12-month clinical study report. New related or unknown adverse events were minimal and mild and included one event for each of the following: odynophagia, inability to vomit, and increased gas. Additionally, there was one event of mild pain with unknown causality.
### Table 11: Summary of New Adverse Events – Related or Unknown at 24 Months

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Mild AEs (n)</th>
<th>Subj. % (n)</th>
<th>Moderate AEs (n)</th>
<th>Subj. % (n)</th>
<th>Severe AEs (n)</th>
<th>Subj. % (n)</th>
<th>Unanticipated AEs (n)</th>
<th>Subj. % (n)</th>
<th>Ongoing AEs (n)</th>
<th>Subj. % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>4</td>
<td>4% (4)</td>
<td>0</td>
<td>0% (0)</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>4</td>
<td>4% (4)</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
<td>0% (0)</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Inability to belch or vomit</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
<td>0% (0)</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
<td>0% (0)</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Other: Increased gas per rectum</td>
<td>1</td>
<td>1% (1)</td>
<td>0</td>
<td>0% (0)</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>1% (1)</td>
</tr>
</tbody>
</table>

### 2. Effectiveness Endpoints and Results

**Primary Endpoint: Normalization or reduction in distal esophageal pH**

Table 12 displays the primary efficacy endpoint. The primary endpoint is a binary outcome of success or failure with success determined by either a normalization of Bravo pH defined as total time ≤ 4.5% at 12 months or a reduction of at least 50% in total time pH ≤ 4 as determined by Bravo pH 12 months from baseline. The specified analysis cohort for the primary efficacy analysis was the treated population which includes all implanted subjects.

The lower 97.5% confidence limit is 53.8% and the p-value for the one-sided, binomial exact test against the null hypothesis that the success rate is ≤ 60% is 0.24.

**Table 12: Primary Efficacy Endpoint: Bravo pH Normalization or ≥ 50% Reduction at 12 Months**

<table>
<thead>
<tr>
<th>Primary Efficacy Endpoint</th>
<th>% Successful (Number of Subjects/Total)</th>
<th>Lower 97.5% Exact Binomial Confidence Limit</th>
<th>p-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bravo pH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Normalization (≤4.5%)</td>
<td>64.0% (64/100)</td>
<td>53.8%</td>
<td>0.24</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● ≥ 50% reduction from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**Secondary Endpoint: Reduction in GERD-HRQL Total Score**

Table 13 displays the number and percent of subjects with a successful reduction of at least 50% in the GERD-HRQL Total Score at 12 and 24 months from the baseline off PPI medication measurement. At 12 months, 92.0% of subjects showed at least a 50% reduction in their
GERD-HRQL Total Score from baseline. At 24 months, 93.3% showed at least a 50% reduction in their GERD-HRQL Total Score from baseline.

**Table 13: Secondary Efficacy Endpoint - ≥ 50% Reduction in GERD-HRQL Total Score from Baseline Off PPI**

<table>
<thead>
<tr>
<th>Secondary Efficacy Endpoint</th>
<th>12-Month Data</th>
<th>24-Month Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Successful</td>
<td>% Successful</td>
</tr>
<tr>
<td></td>
<td>(Number of Subjects/Total)</td>
<td>(Number of Subjects/Evaluated)</td>
</tr>
<tr>
<td>GERD-HRQL: ≥50% reduction</td>
<td>92.0% (92/100)</td>
<td>93.3% (84/90)</td>
</tr>
<tr>
<td></td>
<td>84.8%</td>
<td>86.1%</td>
</tr>
</tbody>
</table>

Patient satisfaction with their current condition is a critical measure of a GERD patient’s response to a treatment. The percentage of subjects satisfied at baseline increased from 0.0% (Off PPI) to 94.7% at 12 months, and 90.0% at 24 months. The percentage of subjects dissatisfied decreased from 95.0% to 3.3% over the same time period, see **Table 14**.

**Table 14: GERD-HRQL Subject Reported Satisfaction with Present Condition**

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

**Secondary Endpoint: Reduction in PPI Medication Use**

**Table 15** displays the number and percent of subjects with a successful reduction of at least 50% in daily PPI use from baseline. At 12 months, 93.0% of subjects showed at least a 50% reduction in their average daily PPI use from baseline. At 24 months, 95.6% of subjects showed at least a 50% reduction in their average daily PPI use from baseline.
Table 15: Secondary Efficacy Endpoint: ≥50% Reduction in Daily PPI Use from Baseline

<table>
<thead>
<tr>
<th>Secondary Efficacy Endpoint 12-Month Data</th>
<th>% Successful (Number of Subjects/Total)</th>
<th>Lower 97.5% Exact Binomial Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI Use: ≥50% reduction in daily use</td>
<td>93.0% (93/100)</td>
<td>86.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>24-Month Data</th>
<th>% Successful (Number of Subjects/Total Subjects Evaluated)</th>
<th>Lower 97.5% Exact Binomial Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI Use: ≥50% reduction in daily use</td>
<td>95.6% (86/90)</td>
<td>89.0%</td>
</tr>
</tbody>
</table>

Other Results:

Esophagitis

The percentage of subjects with no esophagitis increased from 60.0% at baseline to 87.6% at 12 months and 88.7% at 24 months. Grade B esophagitis decreased from 18% at baseline to 3.4% at 24 months. Twenty-two subjects had Grade A at baseline while ten had Grade A at 12 months, and 7 at 24 months. One subject developed Grade D esophagitis at 12 months, which was resolved at 24 months. Esophagitis grade by study visit is provided in Table 16.

Table 16: Esophagitis Grade by Visit

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

Regurgitation Severity and Frequency

At baseline, 91% of subjects experienced regurgitation of varying severity at a mean frequency of 28 times per week. At 12 and 24 months post LINX™ implantation, this mean frequency was reduced to 1 time per week and the prevalence of regurgitation dropped from 91% to 22% of subjects. Most importantly, severe regurgitation, defined as constant and presence of aspirations, dropped from 13% at baseline to 1% at 12 and 24 months post LINX™ implantation, see Table 17.
Table 17: Regurgitation Severity and Frequency

<table>
<thead>
<tr>
<th>Severity</th>
<th>Baseline % (n/N)</th>
<th>Month 12 % (n/N)</th>
<th>Month 24 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>9.0% (9/100)</td>
<td>78.9% (75/95)</td>
<td>77.8% (70/90)</td>
</tr>
<tr>
<td>Mild – After straining and/or large meals</td>
<td>34.0% (34/100)</td>
<td>18.9% (18/95)</td>
<td>21.1% (19/90)</td>
</tr>
<tr>
<td>Moderate – Predictable with position change, straining or lying down</td>
<td>44.0% (44/100)</td>
<td>1.1% (1/95)</td>
<td>0.0% (0/90)</td>
</tr>
<tr>
<td>Severe - Constant regurgitation, presence of aspiration into lungs</td>
<td>13.0% (13/100)</td>
<td>1.1% (1/95)</td>
<td>1.1% (1/90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from BL</th>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>83.2% (79/95)</td>
<td>84.4% (76/90)</td>
</tr>
<tr>
<td>Same</td>
<td>15.8% (15/95)</td>
<td>13.3% (12/90)</td>
</tr>
<tr>
<td>Worsened</td>
<td>1.1% (1/95)</td>
<td>2.2% (2/90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency/Week</th>
<th>Baseline</th>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>99</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Mean±SD (Median)</td>
<td>27.9±61.3 (7.0)</td>
<td>1.2±7.4 (0.0)</td>
<td>0.9±7.4 (0.0)</td>
</tr>
<tr>
<td>Range</td>
<td>0.0, 420.0</td>
<td>0.0, 70.0</td>
<td>0.0, 70.0</td>
</tr>
</tbody>
</table>

Heartburn Severity and Frequency

All heartburn symptoms are not the same. The symptoms of heartburn can vary in severity and frequency. The more severe the heartburn and the more frequent the symptoms, the more significant the impact on quality of life. At baseline, 89% of subjects had moderate or severe heartburn and an average frequency of 79 times per week. This changed to 5.5% of subjects and 2 times per week at 24 months following LINX™ implantation. This observation strongly corroborates an improved quality of life following LINX™ treatment, see Table 18.

Table 18: Heartburn Severity and Frequency by Visit

<table>
<thead>
<tr>
<th>Severity</th>
<th>Baseline % (n/N)</th>
<th>Month 12 % (n/N)</th>
<th>Month 24 % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0% (1/100)</td>
<td>57.9% (55/95)</td>
<td>51.1% (46/90)</td>
</tr>
<tr>
<td>Minimal – Occasional episodes</td>
<td>10.0% (10/100)</td>
<td>38.9% (37/95)</td>
<td>43.3% (39/90)</td>
</tr>
<tr>
<td>Moderate – Primary reason for visit</td>
<td>34.0% (34/100)</td>
<td>2.1% (2/95)</td>
<td>4.4% (4/90)</td>
</tr>
<tr>
<td>Severe – Interfering with activities of daily life</td>
<td>55.0% (55/100)</td>
<td>1.1% (1/95)</td>
<td>1.1% (1/90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from BL</th>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>93.7% (89/95)</td>
<td>91.1% (82/90)</td>
</tr>
<tr>
<td>Same</td>
<td>6.3% (6/95)</td>
<td>8.9% (8/90)</td>
</tr>
<tr>
<td>Worsened</td>
<td>0.0% (0/95)</td>
<td>0.0% (0/90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency/Week</th>
<th>Baseline</th>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>97</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Mean±SD (Median)</td>
<td>78.6±141.5 (35.0)</td>
<td>2.3±8.5 (0.0)</td>
<td>2.0±6.3 (0.0)</td>
</tr>
<tr>
<td>Range</td>
<td>0.0, 700.0</td>
<td>0.0, 56.0</td>
<td>0.0, 42.0</td>
</tr>
</tbody>
</table>
Manometry

Ninety-three subjects completed manometry at the 12 month visit. At 12 months, 15 subjects had <70% effective swallows, and 4 subjects had distal esophageal amplitude <35 mmHg. Clinical relevance of these findings is dependent upon complaints of dysphagia. Only one subject had ongoing complaints of dysphagia and abnormal motility (defined as <70% effective swallows and/or distal amplitude <35 mmHg) at 12 months, see Table 19.

Table 19: Manometry Summary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th></th>
<th>Month 12</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean±SD (Median)</td>
<td>Range</td>
<td>N</td>
</tr>
<tr>
<td>LES resting tone (mmHg)</td>
<td>99</td>
<td>17.5±12.5 (15.4)</td>
<td>0.0, 70.0</td>
<td>93</td>
</tr>
<tr>
<td>LES overall length (cm)</td>
<td>96</td>
<td>3.4±1.3 (3.5)</td>
<td>0.9, 7.7</td>
<td>93</td>
</tr>
<tr>
<td>LES abdominal length (cm)</td>
<td>95</td>
<td>1.6±1.3 (1.5)</td>
<td>-1.5, 5.0</td>
<td>92</td>
</tr>
<tr>
<td>% liquid swallows effective</td>
<td>99</td>
<td>93.6±9.6 (100.0)</td>
<td>70.0, 100.0</td>
<td>93</td>
</tr>
<tr>
<td>LES residual pressure (mmHg)</td>
<td>94</td>
<td>3.8±4.5 (3.0)</td>
<td>-6.3, 22.2</td>
<td>93</td>
</tr>
<tr>
<td>% LES relaxation</td>
<td>50</td>
<td>82.8±19.6 (88.0)</td>
<td>18.0, 103.0</td>
<td>38</td>
</tr>
<tr>
<td>Distal esophageal amplitude (mmHg)</td>
<td>100</td>
<td>78.1±27.4 (72.5)</td>
<td>35.0, 161.0</td>
<td>93</td>
</tr>
</tbody>
</table>

XI. CONCLUSIONS

In conclusion, the efficacy of treatment with the LINX Reflux Management System is demonstrated by the following observations:

- The observed primary endpoint success for the treated population was 64% (64/100) with a 54% lower confidence interval limit. Although the lower bound did not exceed the study success criteria of 60%, a clinically meaningful reduction in pH was seen.

- The mean total acid exposure time was reduced from a pathologic time of 11.3% to 5.1%, or a 55% reduction. Of note, normal total pH % time is <5.3% with the Bravo System; of which, all subject were tested with at baseline and 12 months.

- 90% of subjects reduced their total esophageal acid exposure time;

- 92% of subjects at 12 months and 93 % at 24 months had at least a 50% reduction in total GERD-HRQL scores
93.0% of subjects at 12 months and 95.6% at 24 months had at least a 50% reduction in their average daily PPI dosage

The number of subjects with no esophagitis was increased from 60% at baseline on PPI therapy to 88% at 12 months and 89% at 24 months following LINX implantation;

The number of subjects with Grade B esophagitis was reduced from 18% at baseline to 1% at 12 months and 0% at 24 months following LINX implantation; and,

Subject satisfaction with current their condition at 12 months following the LINX procedure was 95%, and 90% at 24 months.

Treatment of GERD by laparoscopic implantation of the LINX device was shown to be safe in the clinical studies, as evidenced by the low incidence, severity, and transient nature of adverse device and/or procedure related adverse events. No deaths were observed in the clinical studies. There were no device migrations or erosions.

The data generated in our preclinical and clinical studies establish that treatment of GERD by laparoscopic implantation of the LINX device offers an alternative to life-long medical therapy in patients who continue to have chronic GERD symptoms despite anti-reflux drug therapy. In addition, the risks and side-effects associated with the LINX device are substantially lower than surgical intervention or endoscopic plication, with clinically significant health benefits.

The findings of the preclinical and clinical studies confirm the safety and effectiveness of the LINX™ Reflux Management System for the treatment of GERD in the targeted population.

XII. PANEL RECOMMENDATIONS (TO BE COMPLETED BY FDA)

XIII. CDRH DECISION (TO BE COMPLETED BY FDA)

XIV. APPROVAL SPECIFICATIONS (TO BE COMPLETED BY FDA)
V – Proposed Post-Approval Studies
LINX™ Reflux Management System

Clinical Study Protocol

Study ID: 1802

Sponsor: Torax Medical Inc.
4188 Lexington Ave. North
Shoreview, MN 55126

Date of Final Original Protocol: 16-April-2008
Update to follow-up schedules and clarification of inclusion/exclusion criteria, etc. 24-Jun-08
Update to 120 enrollment limit, add dysphagia to risks, eliminate medication log, add eCRFs 31-Jul-08
Update inclusion criteria number 1 from a minimum age of 19 years to "Age of Majority", clarify amount of time screening tests are acceptable: 17-Nov-08
Update inclusion criteria no. 6, PPI scores: 22-Jan-09
Update inclusion criteria 6 and 8, exclusion criteria 13 and 15, 13-Feb-09
Update number of sites and number of enrollments, clarify exclusion criteria 4 and 15, update anticipated adverse events list 12-May-09
Update to extend follow-up schedule to 60 months: 12-Jan-11
Update to incorporate endpoint analysis for the extended follow-up: 08-Nov-11

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APPROVAL OF FINAL PROTOCOL

Torax Medical Inc.
Amy Derosier
Director of Clinical Research

__________________________  ______________________  ________________
Name (print)                      Signature                      Date
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## INVESTIGATIONAL PLAN SUMMARY

<table>
<thead>
<tr>
<th>Study Title</th>
<th>LINX™ Reflux Management System Clinical Study</th>
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<tr>
<td>Study ID</td>
<td>Doc. No. 1802</td>
</tr>
<tr>
<td>Study Device</td>
<td>An implantable single-use LINX device intended to augment the competence of the Lower Esophageal Sphincter (LES) to reduce or eliminate gastric reflux. The device is supplied sterile and is placed through a laparoscopic port.</td>
</tr>
<tr>
<td>Study Purpose/Objective</td>
<td>The purpose of the study is to evaluate the safety and effectiveness of the LINX device in the treatment of Gastroesophageal Reflux Disease (GERD).</td>
</tr>
<tr>
<td>Target Indication for Use</td>
<td>The Torax LINX™ device 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 drug therapy.</td>
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<td>Study Design</td>
<td>The study is a prospective, multi-center, single arm clinical study that will be conducted in the United States and Europe.</td>
</tr>
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<td>Study Duration:</td>
<td>Approximately 6 years (includes time for enrollment and completion of 60 month follow-up).</td>
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<td>Investigational Study Centers</td>
<td>This clinical evaluation will be conducted at up to twenty (20) U.S. investigational Centers and additional European Centers. Investigators will be selected among surgeons with experience performing anti-reflux laparoscopic procedures.</td>
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<tr>
<td>Subject Population</td>
<td>Subjects ages ≥ 18 or Age of Majority according to Law in states or countries where 18 is considered a minor and &lt; 75 years seeking intervention for GERD who meet the study inclusion / exclusion criteria are eligible for this study. The study subject limit will consist of approximately 100 subjects that may be implanted with the device. Subjects entering study will be at least partially responsive to medical therapy (proton pump inhibitors) for their GERD symptoms and have tested positive (abnormal) in esophageal pH testing.</td>
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### INVESTIGATIONAL PLAN SUMMARY (continued)

<table>
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<tr>
<th>Study Endpoints</th>
<th><strong>Primary safety endpoint:</strong></th>
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<td></td>
<td>The primary safety endpoint is the rate of occurrence for serious device and procedure related adverse events. The primary safety endpoint will be assessed by reporting all adverse events and by estimating the rate of serious device and procedure related adverse events through 12 months post implantation. Safety will also be evaluated by endoscopy to assess the mucosa and abdominal/chest X-ray evaluations to verify device location at 12 months post implantation.</td>
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</table>

**Primary effectiveness endpoints:**

Reduction in total distal esophageal acid exposure time defined by esophageal pH testing. Testing will be performed with subjects off PPIs. The subject’s baseline pH acid exposure time will serve as the control and be compared to the subject’s pH acid exposure time 12 months post implantation.

**Success criteria** - At least 60% of subjects will have normalized or improved by at least 50% in total distal acid exposure

**Secondary effectiveness endpoints:**

Subjects GERD-HRQL (Health Related Quality of Life) scores will be assessed off all GERD medications. The subject’s baseline GERD-HRQL score will serve as the control and be compared to the subject’s GERD-HRQL 12 months post implantation.

**Success criteria** - At least 60% of subjects will have a 50% reduction in total GERD-HRQL scores

Subject’s average daily dose of 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.

**Success criteria** - At least 60% of subjects will reduce their average daily PPI dosage ≥50%
### INVESTIGATIONAL PLAN SUMMARY (continued)

| Long-term Safety and Performance Outcomes | **Long-term safety outcome:**  
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.  

**Long-term efficacy outcome:**  
Subjects will be followed to 60 months post-implant to assess the long term efficacy 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.  

**Performance outcome** – A subject will have a 50% reduction in total GERD-HRQL scores  
Subject’s average daily dose of 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  

**Performance outcome** – A subject will reduce their average daily PPI dosage ≥ 50% |
| Additional Information | Procedural information will be recorded at time of subject discharge:  
- Procedural success rate  
- Time of overall procedure  
- Length of hospital stay |
| Sponsor | Torax Medical Inc.  
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Shoreview, MN 55126  
Tel: (651) 361-8900  
Fax: (651)361-8910 |
| Study Management | Torax Medical Inc. or Designate |
1.0 Introduction

1.1 Background – Gastroesophageal Reflux Disease (GERD)

Prevalence

It is well understood that Gastroesophageal Reflux Disease (GERD) is a very serious health condition. GERD, which primarily manifests as heartburn, regurgitation, or both, is a chronic disorder associated with substantial morbidity and potential malignancy. GERD has a major adverse impact on subject’s quality of life. In industrialized nations the disease has become increasingly common, with an estimated prevalence of 7% in the general population based on the presence of daily symptoms.¹

Further the condition often leads to more serious health consequences. When reflux occurs on a chronic basis, it may result in esophagitis (an inflamed lining of the esophagus), narrowing of the esophagus, difficulty in swallowing, chronic sore throat and cough. Of considerable concern is the development of a precancerous condition known as Barrett’s esophagus may develop. Barrett’s esophagus is a condition in which the normal mucosal lining is replaced by an abnormal lining called specialized intestinal metaplasia, a condition that occurs in about 10% of people who have chronic GERD.² Up to 0.5% of patients who have Barrett’s esophagus may develop into esophageal cancer or adenocarcinoma³.

Lagergren, et al, report that the risk of esophageal adenocarcinoma is almost eight times as high among persons in whom heartburn, regurgitation, or both occur at least once a week as opposed to persons without such symptoms⁴.

---

Despite having maximum acid suppression therapy through medications there are still significant voids in the treatment of this disease. As evidence, there was a 216% increase in hospitalizations from 1998 to 2005 with a GERD diagnosis and during this same period of time, the inpatient procedure volume of antireflux surgery has decreased by 27%\(^5\) indicating a patient/physician dissatisfaction with the surgical option. A reported 10-20% of patients are dissatisfied with drug therapy\(^6\). The American Cancer Society estimates that during 2008 approximately 16,470 new esophageal cancer cases will be diagnosed in the United States\(^5\) most coming from patients with Barrett’s esophagus.

### 1.2 Current Treatment Options Including Benefits and Limitations

The normal physiological barrier to GERD is the lower esophageal sphincter (LES) muscle. The LES provides to close the junction between the esophagus and the stomach keeping gastric contents from refluxing into the esophagus. A competent LES keeps the esophagus closed to gastric contents and opens only during swallowing to allow food to pass into the stomach or when belching to allow air out of the stomach. A defective LES is the result of a weak sphincter tone that is insufficient to keep the esophagus closed allowing gastric contents to reflux into the esophagus. The LES may be weak due to poor resting tone, insufficient length, or increased frequency of inappropriate transient relaxations. Given this, the ideal therapeutic approach should aim to restore the functionality of the LES.

GERD is currently treated in one of three ways; drug therapy, endoscopic intervention or surgical intervention. These treatments aim to limit the extent of distal esophageal acid exposure by either reducing the acidity of the refluxing fluids or mechanically modifying the defective LES (endoluminally or surgically).

Drug therapy, which is the most common treatment for GERD, is directed at symptom relief and short term healing of esophagitis. Drugs known as proton pump inhibitors (PPIs), such as Prevacid\(^\circledR\) and Nexium\(^\circledR\), reduce the acid production in the stomach, but do not affect the function of the LES or treat the defective muscle tone, thereby treating the symptoms and not the disease.


These drugs are taken daily but may fail to control the symptoms in 10% to 20% of subjects. Even when symptoms are controlled the esophagus can continue to experience pathological injury.

Importantly, these drugs do not treat the failing LES or eliminate the episodes of reflux. The subject remains vulnerable to the higher risks of progression of the disease and developing adenocarcinoma as well as continued exposure to non-acid reflux (NAR). Frazzoni, et al, reports GERD subjects who were rendered symptom free with PPIs, but the esophageal acid exposure was still abnormal in 44%. Furthermore, Sontag, et al, describe the results of a PPI trial where at 1 year follow-up, 55% to 67% of subjects remained healed (no recurrence of erosive reflux esophagitis), but 62.5% to 73.7% of those who developed erosive esophagus on therapy remained asymptomatic.

Endoscopic procedures have been introduced that attempt to create geometry or compliance changes to the LES by various mechanical techniques including staple plications, bulking implants and radiofrequency energy. These treatments are designed to change the geometry, shape and/or compliance of the LES in order to restore competency to the gastroesophageal junction thereby reducing distal acid exposure. None specifically add functional tone back to the LES barrier. Clinical evaluations have occurred over the past decade to determine the safety and effectiveness of these procedures as well as determine the appropriate patient population suitable for these treatments. The procedure is performed transorally in an anesthetized patient who has moderate GERD with limited or no hiatal hernia. Normalization of esophageal pH exposure, by these endoscopic procedures, has been observed in 23-63% of patients and HRQL improvements of 55-74%. The use of PPI therapy has been reported to be reduced by ≥50% in 51-80% of the patients.

---

The clinical outcomes to date have varied widely indicating a strong dependence on investigator experience and the technique used. Currently the bulking agent (Enteryx – Boston Scientific) and radiofrequency technology (Stretta – Curon Medical) have been removed from the market and a second bulking agent (Gatekeeper - Medtronic) has been discontinued. Plication technology (Plicator - NDO surgical, Esophyx – Endogastric Solutions) remains active in market development. Most recent clinical data on the Esophyx device, which at this time is the only endoscopic technology commercially available, report pH normalization of 34%, GERD-HRQL improvement of 73%, and freedom from daily PPI use of 85%, all at 12 month follow up\textsuperscript{15}.

Surgical intervention or anti-reflux surgery is typically reserved for the most severe GERD patients and is often associated with hiatal hernia repair. The most common anti-reflux surgery is the Nissen Fundoplication which has numerous variations and techniques. Over the years there have been failed attempts to standardize this surgical methodology. Generally in this procedure, the upper portion of the stomach or fundus is dissected and permanently wrapped around the LES region of the esophagus and sutured in place. The fundus is intended to buttress or support a weak LES. Variations include the length, tightness, and geometry of the fundus wrap. Additionally, the fundus wrap is difficult to control; if too much fundus or too tight a wrap is applied, dysphagia occurs and if too little fundus is used or if it is too loose, efficacy may be limited. After surgery, new symptoms occur in approximately 5 to 8% of subjects and may include dysphagia, gas, bloating, increased flatus, and difficulty with belching or vomiting\textsuperscript{6}. Catarci, \emph{et al.} report a recurrence of GERD in up to 10.5% of cases, dysphagia and bloating in up to 57.9% of cases; and re-operation as often as 7.7% of the time\textsuperscript{16}.

The Nissen Fundoplication surgical procedure has a reported efficacy of 73-85% normalization of esophageal acid exposure\textsuperscript{17,18,19}. It is recognized that this reported success rate tends to be derived primarily from specialized, experienced operators which account for only a portion of patient treatments as opposed to procedures performed in the community hospital setting where outcomes are much more variable.

\begin{thebibliography}{9}
\bibitem{15} Lipham J. Medical and Surgical Aspects of Esophageal & Foregut Disorders: Pathophysiology & Treatment Meeting, Hawaii; Oral Presentation with Handout, February 2008
\end{thebibliography}
The surgical outcome is highly dependent on surgeon’s experience and frequently results in new symptoms as outlined above\textsuperscript{20,21}. For these reasons the numbers of Nissen procedures has declined over the last 5 years and it is becoming a procedure primarily for patients with complicated anatomy such as large hiatal hernia and complex GERD. Additionally, the efficacy of the fundoplication may wane over time, with as much as 62\% of subjects requiring medications to control recurrent reflux symptoms 10 years after surgery\textsuperscript{22}.

1.3 Study Rationale

The scientific rationale for the design of the LINX device is based on the premise that subjects with an incompetent (weak) LES will remain susceptible to gastroesophageal reflux until the LES barrier function is restored. The LINX device is designed to augment the LES function and is placed, via a laparoscopic approach, on the external aspect of the esophagus in the region of the LES. The device is comprised of a series of titanium beads with magnetic cores that are linked together with independent titanium wires. As a series, the device forms an annular shape, reference Figure 1.

![Figure 1: Illustration of the Magnetic Esophageal Sphincter](image)

The magnetic attraction of the beads provides a force to augment the LES and to restore its barrier function. When swallowing a bolus, the magnetic force decreases allowing distention of the esophagus and passage of the food bolus.

\textsuperscript{20} Kahrilas P. Laparoscopic Antireflux Surgery: Silver Bullet or the Emperor’s New Clothes? Am J Gastroenterol 1999, 94:7. 1721-1723


The natural function of the LES is to provide a barrier to prevent gastric reflux exposure to the distal esophagus. The “gold standard” objective measure of the degree of the reflux is esophageal pH (acid) monitoring. In this respect, the range of efficacy for all current treatments (anti-reflux surgery, PPI therapy and endoscopic surgery) results in pH normalization of 23-85% of patients. Current data of existing endoscopic treatments which target primarily the same patient population as the LINX device provide pH normalization ranging from 23-63 and most recent data from the only commercially available technology (Esophyx – Endogastric Solutions) reports normalization of 34%. These endoluminal devices have similar procedural requirements of placing a permanent implant, and requiring anesthesia in an operating room setting. The primary effectiveness endpoint in the LINX device study, is defined as at least 60% of subjects will have normalized or improved by at least 50% in total distal acid exposure. Given the minimal risk of a laparoscopic procedure we feel this provides an appropriate level of clinical benefit to the subject population to demonstrate the effectiveness of the treatment when considering alternative therapies for GERD.

Patient symptom improvement (GERD-HRQL) and drug therapy usage will also be analyzed as a secondary measure of success. Based on previous clinical trials of other GERD therapies such as the Medtronic Gatekeeper, the Boston Scientific Enteryx device and the Endogastric Solutions Esophyx device, all implants, efficacy targets for the GERD-HRQL and the drug therapy usage were the following: The average daily proton-pump inhibitor (PPI) average daily dosage was targeted for at least a 50% reduction and GERD-HRQL score were targeted at least a 50% improvement in score. Targets for the secondary endpoints of the LINX study have been set at least 60% of the study population achieving ≥50% reduction in GERD-HRQL and PPI use. In terms of safety, all serious device and procedure related adverse events will be recorded and analyzed.

Torax Medical and our medical advisors believe these endpoints are appropriate and represent clear clinical benefits of restoring the LES barrier function by the relief of symptoms and reduction or elimination of drug therapy dependence for the defined patient population.
2.0 Investigational Device: LINX Device

The implantable single-use device is intended to augment the competence of the Lower Esophageal Sphincter (LES) thereby reduce or eliminate gastric reflux. The device consists of a series of titanium beads with magnetic cores that are linked together with independent titanium wires. Sutures attached to eyelets are secured to form an annular shape at the time of implant, reference Figure 2. The magnetic attraction force of the beads provides the strength to augment an incompetent LES under normal gastric pressure. The device is supplied sterile and is placed through a laparoscopic port with a minimum internal diameter of 10mm.

![Figure 2: Illustration of the Magnetic Esophageal Sphincter](image)

The device can be manufactured to different lengths, based on the number of beads linked together, accommodating the varied esophageal diameters. For purposes of this study, the smallest configuration will have 10 beads, and the largest will have 18 beads. The implant is provided with sutures attached to each end. The attached sutures are used by the physician to secure the ends of the device to each other at the time of implant. The device is implanted on the external aspect of the esophagus in the region of the LES.

**Esophagus Sizing Tool**

A single-use esophagus sizing tool is used at the time of the implant to guide the physician into choosing an appropriately sized device, reference Figure 3.

![Figure 3: Esophagus Sizing Tool](image)

To determine an appropriately sized device for the subject, the Esophagus Sizing Tool is placed on the external aspect of the esophagus in the region of the LES. With the esophagus sizing tool wrapped around the esophagus, the physician is able to select the appropr-
ate device size based on the colored bead which aligns with the white bead, reference Figure 4.

**Figure 4: Esophagus Sizing Tool around the esophagus to determine appropriate sized device.**

The Esophagus Sizing Tool is considered to be a surgical instrument, and will be supplied to the investigative site labeled NON-STERILE. The investigative facility will sterilize the Esophagus Sizing Tool following internal standard sterilization of surgical instruments procedures, and the guidance provided in the *Instructions For Use*.

<table>
<thead>
<tr>
<th>BEAD COLOR</th>
<th>ASSOCIATED DEVICE (BEAD LENGTH)</th>
</tr>
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<tr>
<td>Pre - Orange</td>
<td>10-Bead</td>
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<td>Orange</td>
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<td>3&lt;sup&gt;rd&lt;/sup&gt; Bead Post-Purple</td>
<td>18-Bead</td>
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### 2.1. Target Indication for Use

The Torax LINX™ device 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 drug therapy.
3.0 Study Design and Protocol Overview

The study is a prospective, multi-center, single arm clinical study that will be conducted in the United States and Europe.

The study is intended to evaluate the safety and effectiveness of the LINX device and its ability to augment the barrier function of the LES in GERD patients. The study will be performed at up to 20 investigational centers in the US and additional sites in Europe with approximately 100 subjects being implanted with the device.

The Screening/Baseline Visit will determine the eligibility of subjects to receive treatment with the LINX device.

Subjects will be followed at 48 hours/discharge, 1 week, 3 months, 6 months, 12 months and then annually to 60 months post implantation. The subject will return to the clinic 6 months after surgery for a follow up visit and then again at 12, 24 months and 60 months, reference Figure 5. Additional follow-up via either telephone interview or office visit will be conducted at 1 week, 3 months, 36 months and 48 months post implantation to assess medication use, adverse events and quality of life information. The study follow-up is outlined in Figure 5 and the data collected during all visits are outlined in Figure 6.

Figure 5: Schematic of study design

- **Screening (Baseline Procedures)**
- **Enrollment**
- **Implant**
- **48 hour/Discharge**
- **1 Week Follow-up**
- **3 Month Follow-up**
- **6 Month Follow-up**
- **12 Month Follow-up for endpoint assessments and then annually from 24 months to 60 months**
**Figure 6: Evaluation Schedule**

<table>
<thead>
<tr>
<th>Screening</th>
<th>Implant</th>
<th>48 hour/Discharge</th>
<th>1 Week</th>
<th>3 months</th>
<th>6 months (Office Visit)</th>
<th>12 months (Office Visit)</th>
<th>24 months (Office Visit)</th>
<th>36 months</th>
<th>48 months (Office Visit)</th>
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<td>Adverse Events</td>
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X = Required  
O = Optional
4.0 Study Purpose and Objectives

4.1 Study Purpose/Objective

The purpose of this study is to evaluate the safety and effectiveness of the LINX device in the treatment of Gastroesophageal Reflux Disease (GERD).

5.0 Safety and Effectiveness Measures

5.1 Safety Endpoint

Primary Safety Endpoint:

The primary safety endpoint is the rate of occurrence of serious device and procedure related adverse events. The primary safety endpoint will be assessed by reporting all adverse events and by estimating the rate of serious device and procedure related adverse events through 12 months post implantation. Safety will also be evaluated by endoscopy to assess the mucosa and abdominal/chest X-ray evaluations to verify device location at 12 months post implantation.

The primary safety objective is to estimate the rate of serious, device and procedure related adverse events with a sufficient level of precision, no formal tests of hypothesis will be conducted.

5.2 Effectiveness Endpoints

Primary effectiveness endpoints:

Reduction in total distal esophageal acid exposure time defined by esophageal pH testing. Testing will be performed with subjects off PPI’s. The subject’s baseline pH acid exposure score will serve as the control and be compared to the subject’s pH exposure score 12 months post implantation.

**Success criteria** - At least 60% of subjects will have normalized or improved by at least 50% in total distal acid exposure

Secondary effectiveness endpoints:

Subjects GERD-HRQL (Health Related Quality of Life) scores will be assessed off all GERD medications. The subject’s baseline GERD-HRQL score will serve as the control and be compared to the subject’s GERD-HRQL 12 months post implantation.

**Success criteria** - At least 60% of subjects will have a 50% reduction in total GERD-HRQL scores
Subject’s average daily dose of 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.

**Success criteria** - At least 60 % of subjects will reduce their average daily PPI dosage by at least 50%

### 5.3 Long-term Secondary Endpoints

**Long-term safety endpoint:**
The long-term safety endpoint is the rate of occurrence of 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.

The long-term safety objective is to estimate the rate of serious, device and procedure related adverse events with a sufficient level of precision, no formal tests of hypothesis will be conducted.

**Long-term effectiveness endpoints:**
Subjects GERD-HRQL (Health Related Quality of Life) scores will be assessed off all GERD medications. The subject’s baseline GERD-HRQL score will serve as the control and be compared to the subject’s GERD-HRQL 60 months post implantation.

**Success criteria** - At least 60% of subjects will have a 50% reduction in total GERD-HRQL scores

Subject’s average daily dose of 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 60 months post-procedure.

**Success criteria** - At least 60 % of subjects will reduce their average daily PPI dosage by at least 50%

The long-term efficacy objectives are to assess the efficacy outcomes for durability of response at 60 months post implantation. No formal statistical hypothesis tests will be conducted.

### 5.4 Additional Information

Procedural information will be recorded at time of subject discharge:

- Procedural success rate
- Time of overall procedure
- Length of hospital stay
6.0 **Investigational Study Centers**
Up to twenty (20) US and European investigational centers will be allowed to participate in this clinical study. Investigators will be selected according to appropriate experience performing laparoscopic anti-reflux procedures.

7.0 **Study Population**
The Investigator(s) will be responsible for recruiting individuals to enroll in this study. Only those individuals satisfying the inclusion and exclusion criteria presented below may participate. Any questions regarding subject suitability will be referred to Study Management for review.

7.1 **Inclusion Criteria**
Subjects included in the study must meet all the following criteria:
1. Subject 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 > 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 epigastic 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 for 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 absence of PPI therapy (minimum 7 days)
8. If the subject is of child bearing potential 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
7.2 **Exclusion Criteria**

Subjects will **not be** included in the study if any of the following criteria apply:

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 >3cm 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 follow-up 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 able 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

7.3 **Subject Study Eligibility Process**

Subjects that are being considered for enrollment in this clinical study will be evaluated for eligibility with several pre-operative tests as listed below:

- Esophageal pH
- Manometry/Motility
- EGD Endoscopy
- Barium Esophagram (Fluoroscopy)

At many Investigative Study Centers these tests are performed as part of the normal work-up for a surgical candidate whether they are being considered for antireflux surgery or for participation in this trial.

There also will be study specific testing as prescribed above in Figure 6.0 Evaluation Schedule. These tests are listed below:

- Health History
- GERD-HRQL Questionnaire
- Foregut Symptom Questionnaire
- PPI, H2, Antacid and other Medication Use

While the standard of care for a pre-operative surgical candidate varies from one Investigational Study Center to another. Subjects will be consented before any study specific activities (tests/questionnaires) are administered.

All subjects will undergo the following two part informed consent process.

1) Informed consent for further evaluation to determine eligibility for subject participation in the trial.
2) Informed consent for subjects meeting the eligibility criteria (inclusion/exclusion) granting consent to undergo the surgical placement of the LINX device.
Figure 7: Subject Informed Consent Process

**Study Population Key**

- **Intent to Treat Group**
- **Treatment Group**

**Standard of Care**
Normal Surgical Work-up

(Inform Consent Form I)

Enrolled

**Non-Standard of Care Work-up**
(Study Specific Testing to Determine Eligibility)

Subject Meets all Inclusion/Exclusion Criteria

- Yes
- No

Screening Failure

- Yes
- No

**Surgical Consent form signed**
(Informed Consent Form II)

**Subject**
Meets all Inclusion/Exclusion Criteria

Yes

No

**Implant Procedure**

No

LINX Device Implanted

- Yes
- No

**Procedural Failure**

Patient is followed up for safety endpoint through 3 months

Subject Withdrawn From Study

Follow-up Subject in accordance with protocol

Draft – Revised for Post-Approval Follow-up
8.0 Informed Consent

Prior to Institutional Review Board (IRB)/Ethics Committee (EC) submission, the Investigator will prepare an informed consent form in accordance with this study protocol and all regulatory requirements (e.g. where applicable, 21 CFR Part 50 and in accordance with the Declaration of Helsinki) using the sample informed consent forms provided. A copy of the final IRB/EC approved Informed Consent must be submitted to the Study Management Center prior to starting the study at that investigational center.

Prior to study enrollment, all subjects (or their legal guardian) must document their consent for study participation and authorization for use and disclosure of health information by signing the appropriate IRB/EC-approved Informed Consent Forms.

There will be a two-part consent process. All subjects will sign Informed Consent I prior to undergoing any testing that is being conducted to evaluate their eligibility for implantation of the LINX™ device. Any subject who signs Informed Consent I is considered enrolled even if they do not undergo implantation of the LINX™ device. If subjects do not meet the eligibility requirements for participation based on testing, and/or are excluded based on other criteria they will be considered screening failures and will not be allowed to participate further in the study. These subjects, will not be included in any study endpoint analyses. If subjects meet all eligibility requirements they will need to sign a second consent document (Informed Consent II) which allows the subject to undergo the surgical placement of the LINX device.

The subject will have the opportunity to ask questions of, and receive answers from, the personnel conducting the study.

The Investigator will notify the Study Management Center and the IRB/EC within five (5) working days if device use occurs without subject informed consent.

Prior to follow-up at 24 months post implantation, all subjects (or their legal guardian) must document their consent for continued study participation by signing the appropriate IRB/EC-approved Informed Consent Addendum Form.
9.0 Study Assessments and Data Management

9.1 Demographic and Baseline Assessments

The following information will be collected at baseline/screening visit:

- Date of Birth
- Gender
- Race
- Medical History
- Height
- Weight
- Quality of Life (GERD-HRQL) on PPIs
- Quality of Life (GERD-HRQL) off PPIs (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL with the exception of antacids, which may be taken up until the morning of the visit)
- Foregut Symptoms Questionnaire off PPIs (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit)
- PPI, H2RA, and antacid use
- Esophageal pH testing (If testing is performed within 6 months of implant, subject does not need to repeat test. Subjects shall discontinue any GERD medications for at least 7 days prior to pH testing, with the exception of antacids, which may be taken up until the morning of the visit)
- Hiatal hernia evaluation
- Endoscopy (If testing is performed within 6 months of implant, subject does not need to repeat test)
- Barium Esophagram (If testing is performed within 6 months of implant, subject does not need to repeat test)
- Manometry/Motility testing (If testing is performed within 6 months of implant, subject does not need to repeat test)

9.2 Safety

9.2.1 Safety Measurements: Endoscopy and X-ray

The subject will undergo endoscopy to determine the presence or absence of esophagitis, the length of any hiatal hernia, if present, and to determine if any mucosal damage has occurred. The subject will also have X-rays taken to determine if the device has moved (migrated) from the implant location.
The Los Angeles Classification esophagitis grading scale will be used:

**Los Angeles Classification**

Not present: No Breaks (erosions) in the esophageal mucosa (edema, erythema, or friability may be present.

Grade A: One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length.

Grade B: One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds

Grade C: Mucosal breaks those are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference

Grade 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”

### 9.2.2 Adverse Events

Subjects will be queried at each follow-up regarding adverse events.

The occurrence and device-relatedness of all adverse events will be documented each time the subject is seen; at the Implant/Procedure Visit, 48 hours/Discharge, 6 months, 12 months, 24 months, and 60 months. The subject will also be queried via telephone call or office visit at 1 week, 3 months, 36 months, and 48 months.

### 9.3 Effectiveness Measurements

#### 9.3.1 Esophageal pH

Subjects will undergo esophageal pH testing to determine total distal esophageal acid exposure time.

Normalization for total distal ambulatory esophageal pH testing is defined as:

- pH < 4 for ≤ 4.5% of the time

If longer pH evaluations are received the total distal acid exposure time will be recorded as a 24 hour average (e.g. 48 hour Bravo testing)
9.3.2 GERD–HRQL (Health Related Quality of Life) Scale Questionnaire

A GERD-HRQL Questionnaire will be completed at baseline and at specific follow up visits. (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview.)

**Note:** The GERD-HRQL Questionnaire is to be given prior to any invasive test procedure

The GERD-HRQL is a scale that asks subjects to rate their GERD symptoms on a scale from 0 to 5.

**Scoring Scale:**

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

The following questions are asked:

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?  
11. How satisfied are you with your present condition? Satisfied Neutral Dissatisfied
9.3.3 **GERD Medication Use**

The subject will be asked to report all current GERD medication use at the time of consent and all medications used post implantation throughout all follow-ups. All medications, including those taken for GERD symptoms must be reported. This includes, but is not limited to PPIs, H2RAs and antacids.

9.3.4 **Manometry/Motility**

The subject will undergo manometry/motility to measure LES pressure, length, amplitude of peristaltic contractions, and % effective swallows.

9.3.5 **Barium Esophagram**

The subject will undergo a barium esophagram at baseline to identify any anatomic abnormalities like the presence of strictures, reducibility of a hiatal hernia, and to assess bolus transport.

9.3.6 **Additional Data Analysis - Foregut Symptoms Questionnaire**

A Foregut Symptoms Questionnaire will be completed at baseline and at specific follow up visits. (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview.

**Note: The Foregut Symptoms Questionnaire is to be given prior to any invasive test procedure**

The Foregut Symptoms Questionnaire (Attachment C) asks subjects to grade their possible GERD related symptoms numerically on various scales for each symptom. The following symptoms are graded:

- Heartburn
- Chest pain
- Regurgitation
- Lung problems
- Difficulty swallowing
- Pain with swallowing
- Pain
- Nausea/Vomiting
- Belching
- Bloating
- Increased Gas/Rectum
- Bowel Movements
9.4 Data Management

All study data will be documented on electronic case report forms, which will be provided by the Sponsor or designate. Source documentation must be maintained in each subject’s chart; subject completed questionnaires will be considered their own source document. The coordinator should note that the questionnaires were administered in the subjects chart.

eCRFs and additional subject/study data will be maintained in a secure, password-protected study database.

10.0 Study Procedures

10.1 Roles and Responsibilities

Each investigational center will identify appropriate personnel to perform all study tasks.

10.1.1 Investigator(s)

- This clinician will have responsibility to treat all subjects.
- Document all adverse events that occur during the study.
- Be responsible for signing the CRFs.
- Be responsible for providing medical care to subjects during the study.
- Be required to document experience performing anti-reflux surgery
- Have responsibility for conducting the initial diagnosis and subject enrollment consideration.
- Provide baseline assessments of the subject’s GERD.
- Interview subjects about their GERD symptoms
- Be available for each subject follow-up visit.

10.1.2 Study Coordinator

In addition to the Investigator, a Study Coordinator will be identified at each investigational center to facilitate and manage the study.

10.2 Screening/Baseline Visit

Male or female subjects aged ≥Age of Majority according to State or Country Law to <75 years will be assessed as suitable candidates for this study against the screening inclusion
and exclusion criteria. A log will be kept of all subjects screened for the study but not entered in the study. The reason(s) for excluding these subjects will be recorded.

A signed, dated, informed consent will be obtained from all subjects before any study specific procedures are performed.

The following assessments will be performed at the Screening/Baseline Visit and recorded on the appropriate CRF in order to determine eligibility for entry into the study:

- Date of Birth
- Gender
- Race
- Medical History
- Height
- Weight
- Record health history, female subjects of child bearing age will be given a pregnancy test.
- Review inclusion/exclusion criteria.

All subject records with prerequisite tests should be available prior to implant.

The following assessments and procedures should be completed prior to the implant procedure:

- GERD-HRQL Questionnaire on PPIs
- GERD-HRQL Questionnaire off PPIs (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview.)
- Foregut Symptoms Questionnaire off PPIs (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview.)
- Record details of any prior (over past year) and current medication use.
- Esophageal pH (Subjects shall discontinue any GERD medications for at least 7 days prior to pH testing, with the exception of antacids, which may be taken up until the morning of the visit. A full report including pH tracings along with all six (6) De-Meester components and record what test equipment was used.)
DeMeester Components:

1) % overall time pH <4
2) % upright time pH <4
3) % supine time pH <4
4) Total number of reflux episodes
5) Number of reflux episodes > 5 minutes
6) Longest reflux episode

- Manometry/Motility (Full report documenting all channels and individual amplitudes including tracings)
- EGD Endoscopy (Full report including images of proximal and distal view of esophagogastric junction (EGJ) and, where available, a DVD/CD recording of the entire procedure.)
- Barium Esophagram (Fluoroscopy)-(Full report and, where available, a DVD/CD recording of the entire procedure)

**NOTE:** Subjects are to be off of the following medications prior to surgery as would be consistent with other surgical treatments for GERD including non-steroidal anti-inflammatory medication. The Investigator will decide if blood thinners should be stopped prior to surgery.

### 10.3 Implant

The Investigator will then perform the procedure implanting the LINX device laparoscopically.

The following assessments or procedures must be completed:

- The implant procedure should be recorded on either a DVD/CD
- Record time of overall procedure
- Record any adverse events that occur during the procedure
- EGD Endoscopy is an optional part of the implant procedure that may be used to assess the acute performance of the device by viewing the gastroesophageal junction and the appearance of the valve (Full report including images of proximal and distal view of gastroesophageal junction (GEJ) and, where available, a DVD/CD recording of the entire procedure.)
• An abdominal/chest X-Ray (two views-AP and lateral) will be taken to confirm implant location prior to discharge or no later than 7 days post implant (Hard film or an electronic version and radiologist report regarding device placement).

• Before the subject leaves the hospital, discharge information shall be recorded (length of stay, date of discharge, and drug regimen).

• The subject will be instructed to discontinue any GERD medication.

• The subject shall be reminded of MRI contraindication.

### 10.4 48 Hours/Discharge

The following additional assessment must be completed during this follow-up.

- The subject will be asked about adverse events.

### 10.5 1-Week Follow-up (7 days ± 2 days)

The following assessment must be completed during this follow-up and may be conducted by office visit or telephone:

- The subject will be asked about adverse events.

### 10.6 3-Month Follow-up (90 days ± 30 days)

**Note:** The GERD-HRQL and Foregut Symptoms Questionnaires are to be given prior to any invasive test procedure

The following activities or procedures must be completed during this follow-up:

- GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)

- Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)

- The subject will be asked about current medication use and dosage.

- The subject will be asked about adverse events.
10.7 6-Month Follow-up (180 days ± 45 days)

The following assessments must be completed during this follow-up and must be conducted by office visit:

- GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview). Subjects can complete the GERD-HRQL by telephone or office visit.

- Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview). Subjects can complete the Foregut Symptoms Questionnaire by telephone or office visit.

- The subject will be asked about current medication use and dosage.

- The subject will be asked about adverse events.

10.8 12-Month Follow-Up (365 days ± 60 days)

The following activities or procedures must be completed during this follow-up:

- Health History

- GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview). Subjects can complete the GERD-HRQL by telephone or office visit.

- Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview). Subjects can complete the Foregut Symptoms Questionnaire by telephone or office visit.

- The subject will be asked about current medication use and dosage.

- Esophageal pH (Subjects shall discontinue any GERD medications for at least 7 days prior to pH testing, with the exception of antacids, which may be taken up until the morning of the visit. A full report including pH tracings along with all six (6) DeMeester components as listed in Section 10.2 and record what test equipment was used)
• Manometry/Motility (Full report documenting all channels and individual amplitudes including tracings)
• EGD Endoscopy (Full report including images of proximal and distal view of gastroesophageal junction (GEJ) and, where available, a DVD/CD recording of the entire procedure)
• Barium esophagram (Full report and, where available, a DVD/CD recording of the entire procedure)
• An abdominal/chest X-Ray (two views-AP and lateral) will be taken to confirm implant location. (Hard film or an electronic version and radiologist report regarding device placement)
• The subject will be asked about adverse events.

10.9 24-Month Follow-up (730 days + 60 days)

The following activities or procedures must be completed during this follow-up:

• GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview). Subjects can complete the GERD-HRQL by telephone or office visit.
• Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview). Subjects can complete the Foregut Symptoms Questionnaire by telephone or office visit.
• The subject will be asked about current medication use and dosage.
• EGD Endoscopy (Full report including images of proximal and distal view of gastroesophageal junction (GEJ) and, where available, a DVD/CD recording of the entire procedure)
• An abdominal/chest X-Ray (two views-AP and lateral) will be taken to confirm implant location. (Hard film or an electronic version and radiologist report regarding device placement)
• The subject will be asked about adverse events

10.10 36-Month Follow-up (1,095 days + 60 days)

The following activities or procedures must be completed during this follow-up:
• GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)

• Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview)

• The subject will be asked about current medication use and dosage.

• The subject will be asked about adverse events

10.11 48-Month Follow-Up (1,460 days ± 60 days)

The following activities or procedures must be completed during this follow-up:

• GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview) Subjects can complete the GERD-HRQL by telephone or office visit.

• Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview). Subjects can complete the Foregut Symptoms Questionnaire by telephone or office visit.

• The subject will be asked about current medication use and dosage.

10.12 60-Month Follow-up (1,825 days ± 60 days)

The following activities or procedures must be completed during this follow-up:

• GERD-HRQL Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the GERD-HRQL, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview). Subjects can complete the GERD-HRQL by telephone or office visit.

• Foregut Symptoms Questionnaire (Subjects shall discontinue any GERD medications for at least 7 days prior to completing the Foregut Symptoms Questionnaire, with the exception of antacids, which may be taken up until the morning of the visit or telephone interview). Subjects can complete the Foregut Symptoms Questionnaire by telephone or office visit.

• The subject will be asked about current medication use and dosage.
- EGD Endoscopy (Full report including images of proximal and distal view of gastroesophageal junction (GEJ) and, where available, a DVD/CD recording of the entire procedure).
- An abdominal/chest X-Ray (two views-AP and lateral) will be taken to confirm implant location. (Hard film or an electronic version and radiologist report regarding device placement)
- The subject will be asked about adverse events

### 11.0 Subject Completion and Withdrawal

#### 11.1 Subject Completion

On completion of the study (either by legitimate completion or withdrawal), the investigator will complete the Withdrawal/Completion CRF.

#### 11.2 Subject Withdrawal

A subject may withdraw (or be withdrawn) from the study prematurely for the following reasons:

- Withdrawal of consent by subject
- Serious adverse event (Adverse Event CRF must be completed)
- Protocol deviation
- Lost to follow-up (In case of early withdrawal of a subject, at least three (3) documented attempts should be made to contact the subject and have them come into the clinic).
- Termination of study by the Sponsor
- Investigator believes it is in the best interest of the subject
- Other (must be specified)

The reason for termination will be recorded in the Withdrawal/Completion CRF.

#### 11.3 Subject Screening

A log of all subjects screened for the study but not entered into the study will be maintained by each investigational center. The reason(s) for screening failure of these subjects will be recorded on this log.
Screen failures are those subjects who are not eligible to start treatment following the screening assessment due to failure to meet inclusion and/or exclusion criteria or failure to sign the second consent form (Informed Consent II).

11.4 Treated Subjects

Only those subjects receiving the device (“treated subjects”) will be considered evaluable subjects.

Information on all subjects screened for the study will be recorded. If the subject is not enrolled into the study the reason for exclusion will be documented on the screening log. If the subject is enrolled in the study but the LINX device is not implanted, the reason will be provided on the implant form. Each subject enrolled in the trial will receive an identification number.

12.0 Adverse Events

12.1 Adverse Event Reporting

Starting at the time of implantation and proceeding throughout the duration of the follow-up period, the Investigator will closely monitor each subject for the development of clinical evidence of adverse events.

An adverse event (AE) is an undesirable/unusual experience that occurs to a subject during the clinical study, whether or not considered device related, including, (but not limited to) those events that result from device use as stipulated in the protocol, that appears or worsens during the clinical study. All adverse events that occur during the course of the follow-up period, whether observed by the Investigator or by the subject, and whether or not thought to be device- or procedure-related, will be reported in detail on the appropriate CRF and followed to a satisfactory resolution.

Abnormal assessments that are judged by the Investigator as clinically significant will be recorded as AEs if they meet the definition of an AE. Clinically significant abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal assessment is clinically significant.
The following definitions for rating the severity of adverse events will be used:

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

12.1.1 Relationship to Study Devices/Procedures

The Investigator will also evaluate the relationship to the study device and/or procedure according to the following definitions:

- **Unrelated:** AE is due to the underlying disease state or concomitant medication or therapy not related to the study-specific devices or procedures.

- **Related:** AE had a strong temporal relationship to the study-specific devices or procedures and another etiology is unlikely.

- **Unknown:** Relationship of the AE to the study-specific devices or procedures and alternative etiology is unknown.

12.2 Serious Adverse Events

Adverse events that are defined as “serious”, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning will serve as a guide for defining reporting obligations.

The Investigator must decide whether each event meets the definition of a Serious Adverse Event (SAE). For the purposes of this study, a SAE will be defined as any untoward medical occurrence, whether related to the study device or procedure or not, that meets one or more of the following criteria:

- **Results in death**

- **Is life-threatening**

  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
• Requires subject hospitalization > 24 hours
• Requires prolongation of an existing hospitalization
• Results in persistent or significant disability/incapacity
• Results in fetal distress, fetal death, or a congenital anomaly or birth defect
• Requires intervention to prevent permanent impairment or damage.

All serious adverse events (whether or not considered study-specific device- or procedural-related) must be reported immediately (within 24 hours of discovery) to the Study Management Center.

12.3 Anticipated Adverse Events and Complications

Anticipated adverse events are those events that are reasonably expected to occur as a result of the subject’s disease state, surgery or use of the LINX device.

The following is a list of anticipated adverse events and reactions that may occur. These may include, but may not be limited to the following:

**Risks of general surgery and anaesthesia:**

- Adverse reaction to anaesthesia (headache, muscle pain, nausea)
- Anaphylaxis
- Cardiac arrest
- Death
- Diarrhea
- Fever
- Hypotension
- Hypoxemia
- Infection
- Myocardial infarction
- Nausea
- Odynophagia
- Pneumonia
- Pulmonary embolism
- Respiratory distress
- Thrombophlebitis
- Vomiting
Risks of LINX device implantation procedure and/or device:

- Achalasia
- Bleeding
- Death
- Device erosion
- Device explant/re-operation
- Device failure
- Device migration (device does not appear to be at implant site)
- Diarrhea
- Dysphagia
- Inability to belch or vomit
- 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
- Worsening of preoperative symptoms (including but not limited to dysphagia or heartburn)
12.4 Unanticipated Adverse Device Effects

*Unanticipated adverse device effects* (UADEs) include any serious adverse effects on the health or safety of a subject or any life-threatening problem or death caused by, or associated with, the study device that are not typically associated with the procedure or the investigational device. All unanticipated adverse device effects must be reported to the IRB/EC within 10 working days and to the Study Management Center within 24 hours after the Investigator first learns of the adverse device effect.

13.0 Statistical Analysis Plan

13.1 Sample Size Determination

Minimum sample size requirements are calculated based on the primary efficacy objective using StatXact 5.0 software under an exact, one-sided test for one binomial population. The following hypothesis will be tested

\[
H_0: \pi \leq 0.60 \\
H_a: \pi > 0.60,
\]

where \( \pi \) is the proportion of subjects meeting the success criterion of 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 \( \geq 80\%
- Expected underlying success rate for the treatment group = 75%

Under the assumptions outlined above, a minimum of 80 evaluable subjects are 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 will be 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%.23,24 This level of precision is sufficient to adequately assess the safety of the device and procedure.

13.2 Analysis Methods

Analyses will be conducted according to the principles of Intent-to-Treat and Treated subjects. Subgroup analyses will also be performed.

Study Population Group Definitions (See Section 7.3 Subject Study Eligibility Process)

- **Intent to Treat** - All subjects that meet all of the eligibility criteria and sign the second consent form (Informed Consent II).
- **Treatment** - All subjects that meet all of the eligibility criteria and sign the second consent form (Informed Consent II) and are implanted with the LINX device.

13.3 Descriptive and Demographic Analyses

Continuous demographic and baseline variables of interest will be summarized via standard descriptive statistics (e.g. mean, standard deviation, median, range). Categorical demographic and baseline variables will be summarized via frequency distributions.

**Objective 1: Safety**

**Analysis:** The proportion of subjects free from a serious, device or procedure related adverse event through 3 months will be calculated, along with the corresponding lower 95% confidence limit. In addition, the rate of each type of distinct adverse event will be summarized. Events will be summarized based upon seriousness, expectedness, and the relationship to both the device and the implant procedure. The primary safety analysis will be performed using the Treated study population. Additional analysis will be performed using the Intent to Treat study population.

**Objective 2: Effectiveness**

**Analysis:** The primary efficacy objective will be evaluated by calculating the proportion of subjects meeting the success criterion: pH normalization or at least 50% reduction in distal acid exposure. The lower 97.5% confidence limit of the success rate will be calculated, and if the lower bound is greater than 60%, the objective will have been met. All efficacy analyses, primary and secondary, will be performed using the Treated study population. Additional analyses will be performed using the Intent to Treat study population.

The following secondary objectives will be evaluated. Formal hypothesis tests will be conducted for each objective under a hierarchical closed test proce-
Hypothesis testing on the secondary objectives is dependent on meeting the primary efficacy objectives. All effectiveness:

1. Subjects GERD-HRQL (Health Related Quality of Life) scores will be assessed off all GERD medications. The subject’s baseline GERD-HRQL score will serve as the control and be compared to the subject’s GERD-HRQL 12 months post implantation.

   **Success criteria** - At least 60% of subjects will have a 50% reduction in total GERD-HRQL scores.

2. Subject’s average daily dose of proton pump inhibitor (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 implantation.

   **Success criteria** - At least 60% of subjects will reduce their average daily proton pump inhibitor dosage by at least 50%

Additional, supportive analyses will be conducted, including summaries of all performance outcomes at each study time point.

**Objective 3: Long-term Objectives**

No formal statistical hypotheses will be tested for the long-term objectives. Continued follow-up of the pivotal cohort of subjects will provide sufficient precision to estimate and assess the long-term safety and maintenance of therapeutic effect.

**Safety:**

The proportion of subjects free from a serious, device or procedure related adverse event through 60 months will be calculated, along with the corresponding 95% binomial exact confidence limits. In addition, the rate of each type of distinct adverse event will be summarized. Events will be summarized based upon seriousness, expectedness, and the relationship to both the device and the implant procedure.

**Efficacy:**

The following long-term objectives will be evaluated. No formal statistical hypotheses will be tested. The number and percent of subjects meeting the
stated success criteria will be reported along with 95% binomial exact confidence limits:

1. Subjects GERD-HRQL (Health Related Quality of Life) scores will be assessed off all GERD medications. The subject’s baseline GERD-HRQL score will serve as the control and be compared to the subject’s GERD-HRQL 12 months post implantation.

   **Performance outcome** – A subject will have a 50% reduction in total GERD-HRQL scores.

2. Subject’s average daily dose of proton pump inhibitor (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 implantation.

   **Performance outcome** – A subject will reduce their average daily proton pump inhibitor dosage by at least 50%

### 13.4 Continuous Analysis of Safety Results

Adverse events will be monitored continuously throughout this clinical trial. The analysis will be comprised of summary statistics and confidence intervals, as well as narratives for each subject.

### 14.0 Risk Analysis

The LINX Reflux Management System is manufactured under the Design Control provisions of 21 CFR 820.30 and ISO 13485. It is packaged to meet applicable standards.

#### 14.1 Potential Risks

Complications associated with surgical procedures and device implants have been compiled from the scientific literature and were identified as anticipated adverse events. As with any investigational or approved device, a potential exists for the occurrence of unanticipated adverse events. Torax Medical has no evidence to suggest that the risk of complications associated with use of the LINX device is greater than the risks posed by other existing marketed products/procedures except for those potential risks which are unique to the LINX™ device. See Table 1.
<table>
<thead>
<tr>
<th>Risk</th>
<th>Potential Clinical Effect</th>
<th>Mitigation Measures</th>
<th>Options For Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device migration - up or down esophagus</td>
<td>Device not effective</td>
<td>Animal testing to evaluate device stability</td>
<td>• Remove device&lt;br&gt;• Remove device, convert to fundoplication&lt;br&gt;• Remove device, return to PPI therapy</td>
</tr>
<tr>
<td>Device erosion</td>
<td>• Device not effective&lt;br&gt;• Could effect swallow function&lt;br&gt;• Possible infection</td>
<td>• Device designed to minimize potential erosion&lt;br&gt; • Animal testing to evaluate device stability</td>
<td>• Remove device&lt;br&gt;• Remove device, convert to fundoplication&lt;br&gt;• Remove device, return to PPI therapy</td>
</tr>
<tr>
<td>Device integrity compromised (link breaks)</td>
<td>• Device not effective&lt;br&gt;• Potentially not effective if failure early during healing cycle</td>
<td>• Life cycle testing&lt;br&gt; • Material choices&lt;br&gt; • Manufacturing methods</td>
<td>• Remove device&lt;br&gt;• Remove device, convert to fundoplication&lt;br&gt;• Remove device, return to PPI therapy</td>
</tr>
<tr>
<td>Device integrity compromised (hermetic seal failed)</td>
<td>Tissue response to non-biocompatible material (magnetic core)</td>
<td>• 100% hermetic seal test&lt;br&gt; • Material choices&lt;br&gt; • Manufacturing methods&lt;br&gt; • Surface coat magnetic core with biocompatible material</td>
<td>• Remove device&lt;br&gt;• Remove device, convert to fundoplication&lt;br&gt;• Remove device, return to PPI therapy.</td>
</tr>
<tr>
<td>Magnetic field interaction with electrical implant or metallic, abdominal implants</td>
<td>• Change pacing rate&lt;br&gt; • Suspend ICD therapy</td>
<td>• Labeling (contraindicated for use in subjects with electrical implant or metallic, abdominal implants)</td>
<td>• Subject receives alternative therapy for GERD (fundoplication, PPIs, etc.)</td>
</tr>
<tr>
<td>Toxic Response</td>
<td>Inflammation, infection, foreign body reaction</td>
<td>• Material choices&lt;br&gt; • Manufacturing methods&lt;br&gt; • Biocompatibility testing</td>
<td>• Remove device.&lt;br&gt;• Remove device, convert to fundoplication&lt;br&gt;• Remove device, return to PPI therapy.</td>
</tr>
<tr>
<td>Exposure to MRI</td>
<td>• Large image artifact&lt;br&gt;• Potential direct force on esophagus (acute)&lt;br&gt;• Potential heating on surface of device&lt;br&gt;• Permanent changes to device (magnetic field strength)</td>
<td>• MRI testing to determine effects&lt;br&gt; • Labeling (MRI contraindicated for subjects with device)&lt;br&gt; • Implant card states MRI contraindication</td>
<td>• Remove device.&lt;br&gt;• Remove device, convert to fundoplication&lt;br&gt;• Remove device, return to PPI therapy&lt;br&gt;• Subject receives alternative test to MRI</td>
</tr>
</tbody>
</table>
The proposed study will monitor the subjects at implant, 48 hours/discharge, 1 week, 3 months, 6 months, and 12 months. Furthermore, any risks associated with participation in this clinical study will be minimized and the study will be managed in accordance with 21 CFR 812 Investigational Device Exemptions, 21 CFR 50 Protection of Human Subjects, and 21 CFR 56 Institutional Review Boards, and ICH E6 Good Clinical Practices or current revision. Internationally, ISO 14155-Clinical Investigation of Medical Devices for Human Subjects/Clinical Investigation of Medical Devices and the Declaration of Helsinki.

14.2 Potential Benefits

The potential benefit to subjects being implanted with the LINX device are: to restore the normal function of the LES; to reduce or eliminate GERD related symptoms; and to reduce or eliminate dependence on GERD medications.

14.3 Conclusion

The conduct of this study is not anticipated to pose new types of risks from those identified for similar products/procedures. To date, Torax has no evidence to suggest that the incidence of complications associated with use of its LINX device will be greater than the risks posed by other existing marketed products. Therefore, the potential benefits of the LINX device outweigh the potential risks.

In conclusion, the need for the data from such a study together with the potential benefit of receiving GERD treatment in a controlled setting balances the risk related to participation in this clinical study.

15.0 Protocol Modifications

Neither Torax Medical Inc., its designees (subcontractors or contract research organization), nor the study Investigators may modify this protocol without obtaining written concurrence of each other and the IRB/EC in accordance with the countries regulations (as applicable).

Any deviations from this protocol undertaken to protect the life or physical well-being of a subject in an emergency situation must be reported to the Study Management Center within 48 hours of occurrence and the respective IRB/EC as soon as possible, but in no event later than five (5) calendar days after the emergency occurs.
16.0 Study Materials

16.1 Packaging and Labeling

The LINX device labeling includes Part #, Lot #, Serial #, Use By Date and the statement: “CAUTION—Investigational Device. Limited by Federal (United States) Law To Investigational Use.” Serial numbers will be tracked to ensure traceability of the product.

Labeling describing all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions will be provided in the Instructions for Use supplied with the product. (Attachment B)

16.2 Handling and Storage

The Investigator must ensure that the devices are stored according to the Instructions For Use.

The products are not to be used after the use by date indicated on the label. If a package is damaged, sterility cannot be assured and the contents should not be used. Do not re-sterilize the product.

All supplies are to be used only for this protocol and not for any other purpose. The Investigator must not destroy any unused supply, and is to return all unused product to sponsor.

16.3 Product Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or the head of the medical institution (where applicable), or designated center staff (e.g., storage manager, where applicable) must maintain investigational product accountability records throughout the course of the study.

16.4 Product Implant Technique

LINX Device Implant Technique (See Attachment B - Instructions For Use)

17.0 Study Administration

This study will be conducted in English.
17.1 Institutional Review Board (IRB)/Ethics Committee (EC) Approval

This protocol, Consent Form, and Authorization for the Use and Disclosure of Health Information (as applicable) must be reviewed and approved by the respective IRB/EC and the Study Management Center before subject enrollment. Changes to the protocol must be approved in writing by the Study Management Center and the IRB/EC (as applicable) before the change is implemented.

Prior to subject enrollment, a signed copy of the IRB/EC approval letter addressed to the Investigator must be submitted to the Study Management Center, certifying trial approval. The letter should reference this protocol by title, date and number/revision number as well as the approved Consent Form and HIPAA Authorization (as applicable). Investigators are responsible for submitting and obtaining initial approval and continuing approval from the IRB/EC and forwarding copies of the approval letters to the Study Management Center. The original letters are to be kept in the investigational center Regulatory Document Binder designated for this study.

The Investigator will notify the Study Management Center within five (5) working days of withdrawal of IRB/EC approval.

17.2 Name, Address and Chairperson of each IRB

At the time of this submission no IRBs or ECs have approved the study.

17.3 Name and Address of all Investigators

At the time of this submission, no Investigators have signed an agreement to participate in the study.

17.4 Investigator Agreement and Financial Disclosure

Each Investigator will sign the Investigator’s Agreement before beginning the study, as required by countries’ regulations. The Investigator’s signature signifies his/her willingness to follow the protocol and all regulations and reporting requirements. In accordance with countries’ regulations, all investigators will also be required to sign a Financial Disclosure form, which certifies the Investigator’s and his/her immediate family’s financial interest in Torax Medical Inc. and study outcomes. Investigators must inform the Study Management Center of any changes to the information within the financial disclosure throughout the course of the study and for a period of two years after the device is approved by the FDA or the study is terminated, whichever is later.
17.5 Subject Confidentiality
All information and data sent to Torax Medical Inc. and/or its designees concerning subjects and their participation in this study are considered confidential by Torax Medical Inc. and its designees (subcontractors or contract research organization). Only authorized Torax Medical Inc. personnel or approved contracted agents of Torax Medical Inc. will have access to some portions of these confidential files and will act in accordance with applicable regulations as required by HIPAA (as applicable). The IRBs/ECs and FDA also have the right to inspect and copy all records pertinent to this study. All data used in the reporting of this study will eliminate identifiable references to the subjects.

17.6 Study Management Center
The study will be managed and monitored in accordance with 21 CFR 812, 21 CFR 50, 21 CFR 54, and 21 CFR 56, and ICH E6 Good Clinical Practices or current revision. Internationally, ISO 14155-Clinical Investigation of Medical Devices for Human Subjects/Clinical Investigation of Medical Devices, and the Declaration of Helsinki also apply. Monitors will be restricted to qualified individuals trained in the aforementioned procedures as well as study-related documents. Copies of monitor training records will be maintained at the Study Management Center.

17.6.1 Monitoring Visits
This study will be conducted and monitored in accordance with recognized Good Clinical Practices (e.g. ICH E6 or current revision), 21 CFR 812, 21 FR 50, 21 CFR 54, and 21 CFR 56. Study monitors will be assigned to each site and will be qualified on the basis of education, experience, and training. Study monitors may include Torax Medical personnel, contracted Clinical Research Organization (CRO) personnel, or contracted independent clinical research monitors.

17.6.2 Investigational Center Qualification
Investigational Center qualification visits or phone calls will be conducted by the Study Management Center prior to acceptance of the site into this study. The site qualification visit will be scheduled to include time with the Primary Investigator, co-Investigators, study coordinator, and other study personnel. Areas of discussion include a review of personnel training, Investigator qualifications, adequacy of potential subject pool, research experience,
this study’s specific requirements for procedures and equipment, and a review of staffing and equipment availability and appropriateness. A written report of the qualification visit will be drafted by Study Management. Resolution of any concerns and/or completion of any appropriate study activities identified during the pre-study visit will be documented and submitted to the Primary Investigator.

17.6.3 Site Training

Study-specific training of study personnel is the responsibility of the Study Management Center and the Investigator. Study training will occur before the first device use. To ensure investigational plan and regulatory compliance as well as accurate data collection, site training will include a detailed review of this Investigational Plan, CRF completion, monitoring logistics, and regulatory requirements.

Investigational site study training personnel will ensure that study personnel:

- Submit this Investigational Plan to its IRB/EC and where applicable, the Competent Authority for appropriate review and obtain written approval for the conduct of the study prior to enrolling any subject for this study.
- Maintain all study correspondence, this Investigational Plan, and all related and required records on file at their facility.
- Assume full responsibility for the study investigation at their individual medical practices, clinics, and medical facilities.

17.6.4 Training of Investigators:

Training for Investigators will include some or all of the following:

- Receive materials illustrating the use of the LINX device.
- Perform implantation of the LINX device in one or more animals.
- Observe implantation of the LINX device by another Investigator.
- Be proctored by qualified individuals (Physician or Torax personnel)

All training will be conducted and documented prior to subject enrollment.

17.6.5 Case Report Forms

17.6.5.1 Electronic Case Report Forms (eCRFs)

Standardization of data collection will be achieved through the use of electronic Case Report Forms (eCRFs), which will be completed for each subject.
On completion, eCRFs will be reviewed for accuracy and signed by the physician. Corrections of data on the eCRFs will be made via database. Source documentation must be maintained in each subject’s chart.

eCRFs and questionnaires will be completed for all subjects enrolled in the study. Sites will be requested to complete eCRFs in a timely manner. Any discrepancies will be resolved through data clarifications (queries) with the clinical center.

The Investigator must review, sign and date each eCRF; these responsibilities cannot be delegated to another person. The Investigators are responsible for the accuracy and completeness of all data on the eCRFs.

Completed eCRFs will be reviewed at the investigational site by monitors at regular intervals throughout the study. Information on the eCRFs will be compared to information originally recorded on source documents related to the study (i.e. professional notes, laboratory reports, study-specific worksheets, etc).

A final study closeout visit will be conducted at each investigational site.

17.6.6 Investigator Responsibilities

The Investigator is responsible for ensuring that the study is conducted according to the Investigator Agreement, the Investigational Plan, and all applicable federal regulations for investigational device exemption studies. Specific responsibilities are listed in the Investigator Agreement and this Investigational Plan.

Records and reports must remain on file at the investigational site for a minimum of two years after the later of either the completion/termination of the investigational study or the date the LINX device receives market approval for the indication being studied. They may be discarded only upon approval from Torax Medical. The Investigator must contact Torax Medical before destroying any records and reports pertaining to the study to ensure that they no longer need to be retained. In addition, Torax Medical must be contacted if the Investigator plans to leave the investigational site to ensure that arrangements for a new Investigator or records transfer are made prior to Investigator departure.

Records

Records to be maintained by the Investigator which should be located in the designated regulatory study binder include:

- Investigational plan and all amendments
- Signed Investigator Agreement(s)
- Signed Financial Disclosure form(s)
• IRB/EC approval letter, including consent
• IRB/EC membership list or Letter of Assurance
• All correspondence relating to the study between the site and Study Management
• CVs and professional licenses for all Investigators
• Site personnel signature and responsibility list
• Clinical monitor sign-in log
• Blank set of each version of CRFs
• Subject Screening/Enrollment log
• Deviation log
• Adverse Event log
• Investigational device inventory log including: date, quantity, serial numbers of all devices, identification of all subjects the device was implanted, and final disposition
• Reports (including annual reports and a final report from the investigator)

The following records must be maintained for each subject enrolled in the study:

• Signed Consent Form
• Completed eCRFs and DCFs
• Adverse event reports and any supporting documentation
• Protocol deviations
• Complete medical records, including procedure reports, lab reports, professional notes, etc.
• Records pertaining to subject death during the investigation (including death records, death certificate, and autopsy report, if performed)

Torax Medical Inc. reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study at any time.

**Reports**

Investigators are required as indicated in Table 2 to prepare and submit to the Study Management Center and IRB/EC complete, accurate, and timely reports on this investigation when necessary, according to 21 CFR 812.150, applicable National Laws, and any conditions imposed by the reviewing IRBs, ECs, and/or any other regulatory agencies. Types of reports to be submitted include reports pertaining to unanticipated adverse device effects, withdrawal of IRB/EC approval, and deviations from the investigational plan.
### Table 2 - Reports

<table>
<thead>
<tr>
<th>Report</th>
<th>Submit to:</th>
<th>Description / Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal of IRB/EC Approval</td>
<td>Torax Medical or Designate</td>
<td>Within five (5) working days of withdrawal of approval.</td>
</tr>
<tr>
<td>Deviation from Investigational Plan</td>
<td>Torax Medical or Designate and IRB/EC</td>
<td>Deviations from the Investigational Plan to protect the life or physical well being of a subject in an emergency – submitted within 48 hours to Study Management and no later than five (5) working days after the event.</td>
</tr>
<tr>
<td>Unanticipated Adverse Device Effects</td>
<td>Torax Medical or Designate and IRB/EC</td>
<td>If an unforeseen complication is determined to be an unanticipated adverse device effect, then the Investigators must initially notify the trial monitor within 24 hours and a report must be submitted within ten (10) working days after the Investigator first learns of the effect.</td>
</tr>
<tr>
<td>Use of Device Without Informed Consent</td>
<td>Torax Medical or Designate and IRB/EC</td>
<td>Submitted within five (5) working days after the use occurs.</td>
</tr>
<tr>
<td>Device Related Subject Death</td>
<td>Torax Medical or Designate and IRB/EC</td>
<td>Submitted immediately following the event.</td>
</tr>
<tr>
<td>Submission of Case Report Forms</td>
<td>Torax Medical or Designate</td>
<td>Submitted immediately following the evaluation.</td>
</tr>
</tbody>
</table>

The Investigator is required to submit an annual report to his/her IRB/EC with a copy to the Study Management, and a final report upon completion or termination of this study. The final report must be submitted within 90 days of completion or study termination.

The final report must include:

- Device name
- Number of subjects screened, enrolled, implanted, withdrawn and completed
- Number of devices received, used and returned
- Summary of all adverse events (anticipated and unanticipated)
- Summary of all serious adverse events
- Summary of all protocol deviations
- Summary of results, outcomes, and conclusions
17.6.7 Investigational Site Termination

Torax Medical Inc. reserves the right to terminate an investigational site for any of the following reasons:

- Failure to secure subject informed consent or Authorization for the Use and Disclosure of Health Information prior to study enrollment
- Failure to report unanticipated adverse device effects within 24 hours of discovery (to the Study Management Center) and ten working days (to IRB/EC) of learning of the event
- Failure to report serious adverse events within 24 hours of discovery
- Repeated investigational plan violations
- Repeated failure to appropriately complete CRFs
- Failure to enroll an adequate number of subjects
- Loss of or unaccounted for investigational product inventory
- Administrative decision by the company

18.0 Abbreviations and Definitions

ABBREVIATIONS:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic Case Report Form</td>
</tr>
<tr>
<td>DCF</td>
<td>Data Clarification Form</td>
</tr>
<tr>
<td>DSAE</td>
<td>Device and procedure-related serious adverse event</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act of 1996</td>
</tr>
<tr>
<td>H2RA</td>
<td>Histamine type 2 receptor antagonist</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IRB/EC</td>
<td>Institutional Review Board/ Ethics Committee</td>
</tr>
<tr>
<td>LES</td>
<td>Lower esophageal sphincter</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>UADE</td>
<td>Unanticipated Adverse Device Effect</td>
</tr>
</tbody>
</table>

DEFINITIONS: None
## Document Change History

<table>
<thead>
<tr>
<th>Document Revision</th>
<th>DCO Number</th>
<th>Reason For Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>169</td>
<td>New Release</td>
</tr>
<tr>
<td>2</td>
<td>201</td>
<td>Update to follow-up schedules and clarification of inclusion/exclusion criteria, etc.</td>
</tr>
<tr>
<td>3</td>
<td>214</td>
<td>Update to include up to 120 enrollments, add dysphagia to section 13.2, update to eCRFs.</td>
</tr>
<tr>
<td>4</td>
<td>278</td>
<td>Update inclusion criteria number 1 from a minimum age of 19 years to “Age of Majority”, clarify amount of time screening tests are acceptable.</td>
</tr>
<tr>
<td>5</td>
<td>312</td>
<td>Update inclusion criteria number 6 from “Subjects with symptomatic improvement on PPI therapy demonstrated by an GERD-HRQL score of $\leq 10$ on PPI and $\geq 15$ off PPI” to “Subjects with symptomatic improvement on PPI therapy demonstrated by a GERD-HRQL score of $\geq 15$ off PPI therapy and the GERD-HRQL score on PPI therapy must be less than the off PPI therapy score”</td>
</tr>
<tr>
<td>6</td>
<td>335</td>
<td>Update inclusion criteria 6 from “Subjects with symptomatic improvement on PPI therapy demonstrated by a GERD-HRQL score of $\geq 15$ off PPI therapy and the GERD-HRQL score on PPI therapy must be less than the off PPI therapy score” to “Subjects with symptomatic improvement on PPI therapy demonstrated by a GERD-HRQL score of $\leq 10$ on PPI and $\geq 15$ off PPI, or subjects with a $\geq 6$ point improvement when comparing their on PPI and off PPI GERD-HRQL score”, update inclusion criteria 8 to state pregnancy test must be before implant, update exclusion 13 and 15 to include “history of or known” disease states.</td>
</tr>
<tr>
<td>7</td>
<td>363</td>
<td>Update number of sites and number of enrollments, clarify exclusion criteria 4 and 15, update anticipated adverse events list</td>
</tr>
<tr>
<td>8</td>
<td>637</td>
<td>Increase follow up period.</td>
</tr>
</tbody>
</table>
19.0 References


15. Lipham J. Medical and Surgical Aspects of Esophageal & Foregut Disorders: Pathophysiology & Treatment Meeting, Hawaii; Oral Presentation with Handout, February 2008


ATTACHMENT A: INFORMED CONSENT FORM

ATTACHMENT B: INSTRUCTIONS FOR USE

ATTACHMENT C: CASE REPORT FORMS
LINX™ Reflux Management System:  
Post Approval Study

Protocol

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APPENDICES

Appendix A: Instructions for Use (IFU) for the LINX Reflux Management System
Appendix B: Informed Consent for Post Approval Study (Template)
Appendix C: Case Report Forms (CRFs)
1.0 INTRODUCTION

Gastroesophageal Reflux Disease (GERD) is the most prevalent gastrointestinal disease in the USA and probably the most important in terms of chronic debility, cancer risk and overall cost.\(^1\)

In addition to painful or discomforiting symptoms, GERD may result in mucosal injuries of the esophagus ranging from inflammation to ulcerations. This mucosal injury may also lead to a pre-cancerous condition known as Barrett’s esophagus. It is estimated that 20% of patients with chronic GERD will develop Barrett’s esophagus, with an associated .05% to 1% per year risk of developing adenocarcinoma.

Although the pathogenesis of GERD is complex and mutli-factorial, central to its development is a weak or defective junction between the stomach and esophagus often termed the gastroesophageal junction or (GEJ).\(^{ii,iii}\) The GEJ, formed by a muscular structure called the lower esophageal sphincter (LES) and the crura of the diaphragm, functions as an anti-reflux barrier. The effectiveness of this barrier is dependent on muscle tone or “squeeze” of the LES and the extrinsic muscular element of the crural diaphragm. In GERD, the LES may have decreased resting tone (i.e., be hypotensive), or it may exhibit transient LES relaxations (TLESRs). A hypotensive LES indicates the squeeze of the sphincter is weak and will yield more easily to gastric pressures, causing reflux. With TLESRs, the LES has normal resting tone and length, but gastric distention after eating or intragastric pressure is thought to transiently relax the sphincter allowing reflux.

The LINX Reflux Management System was evaluated in two FDA approved IDE trials. In totality, the information from these two trials includes 144 subjects with follow-up data between two and four years. The results of these trials show the LINX device safely and effectively treats GERD in those patients with an incomplete response to PPI therapy. There were no operative complications or unanticipated adverse device effects (UADEs).

The Food and Drug Administration granted approval for the LINX™ Reflux Managements System on XXXX with the stipulation that a post-approval study be conducted to evaluate outcomes. Data from subjects implanted in this study will be analyzed to evaluate long-term safety and effectiveness of the LINX™ Reflux Management System in the treatment of GERD symptoms.
2.0 BACKGROUND

The LINX™ Reflux Management System is intended for use in the treatment of symptoms associated with Gastroesophageal Reflux Disease (GERD). The LINX device is placed at the area of the Lower Esophageal Sphincter (LES) designed to augment a weak LES and minimize or eliminate GERD related symptoms. The LINX 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 drug therapy. The Indications and Contraindications from the LINX’s Instructions for Use (IFU) will provide the basis for screening potential study subjects (see Appendix A for IFU).

3.0 OBJECTIVES

The LINX Post Approval Study is designed to supplement existing safety and efficacy data regarding the use of the LINX Reflux Management System in the treatment of GERD related symptoms. The primary safety and efficacy objectives are:

- To provide long-term safety information on subjects implanted with the LINX device
- To demonstrate long-term clinical efficacy in the reduction of GERD related symptoms in subjects receiving the LINX implant

4.0 STUDY ENDPOINTS

4.1 Safety

The primary safety endpoint is serious, device related adverse events. The primary safety objective will be analyzed by reporting all serious device related adverse events and summarizing by the number of events, the number of subjects with event and the percent of subjects implanted with event. No formal statistical hypothesis tests will be conducted.

4.2 Efficacy

The primary efficacy objective will be successful reduction of $\geq 50\%$ in the total GERD-HRQL score at 36 months as compared to baseline. The primary efficacy objective will be analyzed according to the following hypotheses:

$$H_0: \Pi \leq 60\%$$
HA: $\Pi > 60\%$,

where $\Pi$ is the percent of subjects with a reduction of $\geq 50\%$ 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. The required sample size was calculated using SAS v9.2 under the following assumptions:

- Type I error = 2.5%
- Assumed success rate = 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.

5.0 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 efficacy of the LINX Reflux Management System. Implanted subjects will be followed for 36 months. Up to 25 sites will participate and a maximum of 200 subjects will be implanted.

Subjects will be considered enrolled at the time of implant. The expected date of study initiation is <date>. With approximately xx study sites with IRB approval enrolling in any given month and an expected monthly enrollment of x-x subjects per month per site, the total monthly enrollment is expected to be xx until the maximum enrollment of 200 subjects is achieved by approximately <date>. The expected date the study required follow-up will be completed is approximately 36 months following the final implant, <date>. Following final data collection and analysis, the Final Report would be submitted by <date>.
SCHEMATIC OVERVIEW OF LINX POST APPROVAL STUDY

LINX Surgical Candidate

*Pt chronic GERD Symptoms despite anti-reflux therapy and abnormal esophageal pH*

Informed Consent

Screening Form & Pre-Surgical Questionnaires

Surgical and Discharge Form

Healthcare Utilization, Meds and AE Form (12-m, 24-m, 36-m)

Post-Surgical Questionnaire (12-m, 24-m, 36-m)

STUDY COMPLETE
6.0 SUBJECT ELIGIBILITY

7.1 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.

7.2 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)

7.0 PROCEDURE
When implanting the LINX System, the considerations provided in the IFU for surgical access, sizing of the esophagus, and placement of the implant device should be followed.

8.0 BENEFITS AND RISKS

9.1 Benefits
The study provides no direct benefit to subjects and does not require any additional invasive tests or procedures not already planned as part of the subject’s individualized treatment plan.

9.2 Risks
The study involves the use and disclosure of health information. Only information relevant to the study’s objectives will be collected. The risk of providing this health information is believed to be minimal as information directly identifying the subject will not be collected for the study. Specifically, the identifiers listed below will NOT be collected as part of this study:
- Name
- Postal address information including city, state and zip code
- Telephone or fax numbers
- Email addresses
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate or license numbers
- Vehicle identification and serial numbers
- URLs and IP addresses
- Biometric identifiers (fingerprints, retinal scans, etc.)
DRAFT

- Full face photos and comparable images

Data will be tracked in the study database using only ID numbers and subject initials. The information submitted will not be associated with a specific subject's identity.

Any potential procedural risks are not changed by participation in the study. The treating physician, as with any gastroesophageal surgery, is expected to counsel the subject on the risks and benefits specific to the planned treatment and obtain the appropriate procedure-related informed consent per institutional policy and procedure.

The study does not increase a subject’s exposure to physical harm because no invasive or radiologic assessments are required. Subjects are expected to undergo the same routine pre-operative and post-surgical evaluations as would be performed regardless of participation in the study.

9.0 SUBJECT ELIGIBILITY PROCESS

Subjects being considered for enrollment in this clinical study will be evaluated for eligibility as outlined in the LINX’s IFU. Any study specific testing or questionnaires will be administered after the subject has provided written informed consent. Prior to Institutional Review Board (IRB), the Investigator will prepare an informed consent form in accordance with this study protocol and all regulatory requirements (e.g. where applicable, 21 CFR Part 50 and in accordance with the Declaration of Helsinki) using the sample informed consent forms provided. A copy of the final IRB approved Informed Consent must be submitted to the Sponsor prior to starting the study at that investigational center.

Prior to study enrollment, all subjects (or their legal guardian) must document their consent for study participation and authorization for use and disclosure of health information by signing the appropriate IRB/EC-approved Informed Consent Forms.

The subject will have the opportunity to ask questions of, and receive answers from, the personnel conducting the study.

10.0 CONFIDENTIALITY

To maintain subject confidentiality, all subject information entered into the study database is referenced by subject identification (SUBJECT ID) numbers and initials only. If supplemental laboratory or imaging reports are submitted, the subject’s name or other prohibited identifiers must be deleted and the subject ID number and initials added to each item. A subject’s privacy and personal health information will be protected as required by law.

11.0 SITE SELECTION

Sites interested in participating in the study will be assessed for their ability to fully and appropriately participate. In general, sites will be selected if subject volume is adequate to support enrollment and follow-up, and the participating physician(s) are qualified by education and training. <need to address site/subject recruitment>

12.0 SITE START-UP DOCUMENTATION

A site will not be permitted to enroll subjects or enter data into the study database until the following documentation is on file at Torax Medical:
• LINX product training confirmed for all investigators listed on the application
• Post Approval Study training satisfactorily completed for the Principal Investigator and any
designees involved with the Post Approval Study
• Receipt of IRB approval
• Signed Investigator Agreement
• Current signed Curriculum Vitae for all investigators listed on the Investigator Agreement
• Financial disclosure for all investigators listed on the Investigator Agreement

13.0 DATA COLLECTION AND SUBMISSION

14.1 Case Report Form-based Data Collection

Initially, the data collected in the LINX Post Approval Study will be collected on Case
Report Forms (CRFs). It may be possible that Torax will progress to an internet-based
electronic data capture (EDC) system as defined in Section 14.2.

14.2 EDC System

The LINX Post Approval Study may progress to an internet-based EDC system utilizing
electronic case report forms, administered through a secure website, to collect data.

The data may be entered by the participating physician and/or designee (such as a study
coordinator) after completing training for the Post Approval Study. Sites have real-time
review of data collected at their site.

14.3 Data Points for Collection

The data to be collected is intended to reflect information typically found in the medical
record and surgical report for a subject undergoing, and being followed for, surgical
treatment of GERD with the LINX device.

Information to be collected in the Post Approval Study is provided on the CRFs
(Appendix C) and includes the following:

• Study screening and qualification
• Demographics, including date of birth
• Pre-Surgery Questionnaire, to be completed by the subject, assessing GERD
symptoms and primary reason for implant
• GERD medications including type and frequency of use
• Baseline characteristics (hiatal hernia size, esophagitis, confirmation of abnormal
esophageal pH, for example)
• Device and surgical procedure data: admission and discharge dates, surgical
procedure times, device information, and concomitant surgical procedures
• Post-Surgical Questionnaire, to be completed by the subject, assessing GERD
symptoms and satisfaction
• Device and/or procedure related Adverse Events
• Healthcare resource utilization including details about treatment, hospitalizations,
and visits to the emergency department and/or physician’s office related to GERD
or procedural complaints/complications
14.4 Effectiveness Measurements

**GERD-HRQL (Health Related Quality of Life) Questionnaire**

A GERD-HRQL Questionnaire will be completed at baseline and at specific follow up assessments. The GERD-HRQL is a scale that asks subjects to rate their GERD symptoms on a scale from 0 to 5.

Scoring Scale:
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

The following questions are asked:

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?  
11. How satisfied are you with your present condition? Satisfied/Neutral/Dissatisfied

**GERD Medication Use**

The subject will be asked to report all current GERD medication use at baseline prior to implant, and post implantation at each follow-up assessment. Subjects’ PPI medication use will be assessed for significant reduction from baseline. A subject will be determined to have achieved a successful reduction in PPI medication if the follow-up dose is reduced by $\geq 50\%$.

14.5 Schedule of Data Collection

The time points for data collection and the data to be collected are depicted in Table 1. The Pre-Surgical and Post-Surgical Questionnaires can be administered over the phone or sent by mail and does not require an office visit. All Follow-up visits have a +/- 60 day visit window and can be conducted by phone.
Table 1. Schedule of Data Collection

<table>
<thead>
<tr>
<th>Pre-Operative</th>
<th>Data Collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Demographics</td>
</tr>
<tr>
<td></td>
<td>Baseline Screening</td>
</tr>
<tr>
<td>R1</td>
<td>Pre-surgery and GERD Questionnaire³</td>
</tr>
<tr>
<td>R</td>
<td>Surgery/Discharge Data</td>
</tr>
<tr>
<td>R2 R2 R2</td>
<td>Abdominal/Chest X-ray</td>
</tr>
<tr>
<td>R2 R2 R2</td>
<td>Post-surgery and GERD Questionnaire³</td>
</tr>
<tr>
<td>R R R R</td>
<td>Healthcare Resource Utilization</td>
</tr>
<tr>
<td>R R R R</td>
<td>GERD Medications</td>
</tr>
<tr>
<td>R R R R</td>
<td>Serious Adverse Events</td>
</tr>
</tbody>
</table>

* 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

14.6 Data Submission

Data should be submitted in a timely manner as data becomes available. Prompt submission of data enables better tracking of enrollment and earlier identification of missing data, discrepancies, or adverse events requiring follow-up.

14.0 QUALITY ASSURANCE OF DATA
The Principal Investigator is responsible for assuring that accurate and complete data are collected and entered into the study database. Data will be reviewed periodically by Torax Medical for missing data points, incomplete information, and discrepancies. When necessary, issues will be resolved by electronic mail, telephone, facsimile, or site visit. All data management and analysis will occur in a validated computing environment.

A study monitor will maintain active and ongoing contact with each site and its participating investigator. Random audits of data may occur against source documentation. Each site will maintain retrievable source documents for all subjects enrolled in the study until notified by Torax Medical in writing that record retention is no longer necessary.

15.0 STATISTICAL METHODS

16.1 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.

16.2 Primary Safety and Efficacy 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 efficacy objective will be summarized as the number and percent of subjects assessed at 36 months follow-up who demonstrate a $\geq 50\%$ reduction in the total GERD-HRQL score from baseline. The associated 95% binomial exact confidence limits will also be calculated.

16.3 Handling of Missing Data
Subjects who withdraw from the study seeking alternative treatment will be included in the primary efficacy 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.

16.0 ADVERSE EVENT REPORTING
Torax Medical is responsible for collecting, reviewing, and communicating relevant information to regulatory authorities regarding adverse events related to the LINX System. During the Post Approval Study, participating sites are expected to monitor and report adverse events to Torax Medical that are deemed by the physician to be device and/or procedure related.

For purposes of the Post Approval Study, an adverse event is defined as an undesirable experience associated with the LINX System that requires the subject to seek medical attention for evaluation or treatment. A list of potential complications related to the LINX Reflux Management System can be found in the Instructions for Use (IFU).
Adverse events requiring an intervention, such as esophageal dilation or surgical revision, for example, should be reported to the Sponsor within 10 working days of the intervention. Serious adverse events (SAEs) related to the LINX System should be reported to Torax Medical within 24 hours of knowledge of the event. An event is considered serious if it meets one or more of the following criteria:

- Is life-threatening or results in death
- Requires hospitalization >24 hours
- Requires prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in fetal distress, fetal death, or congenital anomaly or birth defect
- Requires intervention to prevent permanent impairment or damage

17.0 STUDY REPORTS

Study Progress Reports will be submitted to the Food and Drug Administration at 6, 12, 18 and 24 months from study initiation and annually thereafter, as necessary. A Final Report will be submitted at the conclusion of the study.

18.0 REIMBURSEMENT

There is no financial incentive to the subject to undergo treatment with the LINX System. The subject and/or health care payer are responsible for payment in the customary manner, including payment for costs related to complications.

19.0 REFERENCES


<table>
<thead>
<tr>
<th>Document Revision</th>
<th>DCO Number</th>
<th>Reason For Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>New Release</td>
</tr>
</tbody>
</table>


VI – Proposed Post-Approval Training Programs
Summary of Proposed Post-Approval Training Programs

Torax Medical is committed to ensure that the LINX System is used appropriately and safely post-approval. Torax Medical 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 comprehensive 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.

Additionally, Torax Medical intends to establish a Training Advisory Panel of at least 3-5 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. The Advisory Panel is consistent with Torax Medical’s history of partnering and collaborating with clinicians to further advance the treatment of GERD in a responsible and safe manner. Responsibilities of the Advisory Panel may include: 1) establishing training and certification requirements, 2) working in collaboration with Torax Medical to develop training materials suitable for the intended audience, 3) reviewing complaints and adverse events reported through the customer complaint system, and 4) providing continued assessment of the quality and effectiveness of the training programs established by Torax Medical.

Table: Training Programs

<table>
<thead>
<tr>
<th>Program</th>
<th>Objective</th>
<th>Primary Curriculum</th>
<th>Resources to be made available</th>
</tr>
</thead>
</table>
| Physician Training | Provide training to referring physicians and implanting surgeons that enables and promotes the safe and proper use of the LINX device | - Patient selection  
- Implant procedure  
- Post-implant management and care  
- Reporting of complaints and adverse events to the Torax Medical | - Written materials  
- Video/web program  
- Hands on Use and Demonstration  
- Proctoring of cases  
- Certification Program  
- Post-Training Follow-up |
| Patient Education      | Provide potential patients with easy to understand information about the LINX device, procedure and post-implant expectations to enable informed decisions and participation in care | - Who is the LINX device indicated for  
- Potential benefits  
- Potential risks  
- What to expect after the implant procedure  
- How to register the implant device | - Educational brochures  
- Torax website  
- Implant card for wallet  |