

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Endoscopic Implantation of Enteryx™ for the Treatment of Gastroesophageal Reflux Disease (GERD)

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I. GENERAL INFORMATION

- A. Device Generic Name:** EVOH-T (Ethylene Vinyl Alcohol Copolymer with Tantalum)
- B. Device Trade Name:** Enteryx?
- C. Applicant's Name and Address:** Enteric Medical
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- D. Date of Panel Recommendation:** TBD
- E. Premarket Approval Application (PMA) Number:** PMA Shell M010024
- F. Date of Good Manufacturing Practice Inspection:** TBD
- G. Date of Notice of Approval to Applicant:** TBD

II. INDICATIONS FOR USE

Enteryx™ is indicated for endoscopic injection into the lower esophageal sphincter (LES) for the treatment for gastroesophageal reflux disease (GERD).

III. DEVICE DESCRIPTION

Enteryx is a medical device comprised of an injectable solution of ethylene vinyl alcohol copolymer (EVOH) dissolved in dimethyl sulfoxide (DMSO). Upon contact with polar physiologic fluid, the DMSO solvent diffuses away, resulting in solidification of the hydrophobic copolymer, which forms a spongy solid mass. The liquid Enteryx polymer is delivered endoscopically into and along the muscle layer of the lower esophageal sphincter (LES) via a sclerotherapy type catheter.

The Enteric Medical Technologies, Inc. Enteryx System for the treatment of gastroesophageal reflux disease (GERD) is comprised of:

- ?? One 10 cc glass vial of sterile Enteryx solution.
- ?? One 10 cc glass vial of sterile dimethyl sulfoxide (DMSO) for priming the injection catheter.

Accessories

- ?? One Enteryx Injection Catheter, for injecting the Enteryx solution.
- ?? Two DMSO compatible sterile syringes for priming and loading the Injection Catheter with DMSO or Enteryx.
- ?? Two DMSO compatible sterile needles for use with the syringes.

The Enteryx? solution consists of a biocompatible polymer, 8% Ethylene-Vinyl Alcohol copolymer (EVOH), dissolved in dimethyl sulfoxide (DMSO) as the solvent. Micronized tantalum powder (30%) is added to the polymer/solvent mixture to serve as the contrast for visualization under fluoroscopy. Upon injection through a syringe and contact with aqueous body fluids, the solvent rapidly diffuses away causing *in-situ* precipitation of the polymer and formation of a spongy mass.

The liquid Enteryx material is delivered via an injection catheter to the lower esophageal sphincter. The liquid quickly transforms into a solid spongy mass as the DMSO solvent diffuses into the blood and interstitial spaces.

Enteryx is packaged as 10 ml of sterile product in a glass vial. DMSO, the solvent for priming the injector, is also packaged as 10 ml of sterile product in a glass vial. The vials are sealed with Teflon-lined silicone stoppers and aluminum closures. Enteryx is used with DMSO-compatible disposable sterile syringes, injectors, and needles provided by Enteric Medical.

IV. CONTRAINDICATIONS & PRECAUTIONS

A. CONTRAINDICATIONS

Enteryx must not be used in patients with portal hypertension.

B. PRECAUTIONS

The safety and effectiveness have not been established in patients with Barrett's epithelium, scleroderma, esophageal motility disorders, esophageal or gastric cancer, large hiatal hernias,

prior gastric or GERD surgery, persistent high grade esophagitis, esophageal or gastric varices, gross obesity, or immune suppressant therapy. The safety and effectiveness have not been established in women who are pregnant or lactating.

V. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following device-related adverse events were observed during the clinical study:

- ?? Retrosternal chest pain
- ?? Dysphagia
- ?? Fever
- ?? Belching/burping
- ?? Bloating/flatulence
- ?? Body odor/bad taste
- ?? Rib pain
- ?? Flu syndrome

The following procedure-related adverse events were observed during the clinical study:

- ?? Pharyngitis
- ?? Nausea and vomiting
- ?? Nausea
- ?? Shoulder pain
- ?? Dry mouth
- ?? Anxiety
- ?? Breast pain

There were no unanticipated adverse device effects reported during this investigation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices and procedures available for the treatment of GERD include:

- ?? Drug therapy with proton pump inhibitors (PPIs), such as Prilosec® and Prevacid®
- ?? Drug therapy with H₂ receptor antagonists, such as Pepcid®, Tagamet®, and Zantac®
- ?? Antireflux surgery
- ?? Diet modification

VII. MARKETING HISTORY

Enterix received the CE mark in May 2000, at which time limited marketing of the device in select European countries began. Enterix has not been withdrawn from marketing for any reason related to the safety and effectiveness of the device.

VIII. SUMMARY OF NON-CLINICAL STUDIES

A. **BIOCOMPATIBILITY TESTING**

Biocompatibility testing of Enterix (EVOH-T) was performed according to the requirements of ISO 10993-1 for permanent implants. This testing included cytotoxicity (MEM elution) of EVOH-T and DMSO alone, sensitization by guinea pig maximization (Magnusson/Kligman), USP intracutaneous reactivity, USP acute systemic toxicity, subacute toxicity, and acute rabbit intramuscular implant (seven days). Chronic toxicity of EVOH with and without tantalum was evaluated in rabbits. Genotoxicity testing, including Ames reverse mutation, mouse lymphoma cell, and mouse micronucleus test, was also performed. The results of these tests demonstrate that Enterix is non-toxic and biocompatible. A summary of the biocompatibility testing is presented in *Table 1*.

Biocompatibility Testing for EVOH-T and EVOH

Test Description	Title	Results
Cytotoxicity	MEM Elution Test Evaluation of EVOH-T	No evidence of cytotoxicity
Cytotoxicity (DMSO Only)	MEM Elution Test Evaluation of DMSO (Dilution Series)	No evidence of cytotoxicity
Sensitization	Evaluation of EVOH-T by Guinea Pig Maximization (Magnussen/Kligman Method)	Grade I weak response, equivalent to negative control
Intracutaneous Reactivity	USP Intracutaneous Reactivity Evaluation of EVOH-T	Met USP requirements
Acute Systemic Toxicity	USP Acute Systemic Toxicity Evaluation of EVOH-T	Met USP requirements

Test Description	Title	Results
Subacute Toxicity	Fourteen-Day Subacute Intravenous Dosing Study of EVOH-T in Mice	Non-toxic
Muscle Implantation	USP Seven Day Muscle Implant Evaluation of EVOH-T	USP requirements not met due to acute tissue response
Chronic Toxicity	One Year Intramuscular Implant Evaluation of EVOH and EVOH-T in Rabbits	Stabilized as mild inflammatory response; non-toxic
Genotoxicity	Bacterial Reverse Mutation Assay Conducted with Test Article Extracts – EVOH-T	Extracts were negative, passed
Genotoxicity	In Vitro Mammalian Cell Gene Mutation Test Conducted with Test Article Extracts – EVOH-T	Extracts were negative, passed
Genotoxicity	Micronucleus Cytogenetic Assay in Mice Conducted with Test Article Extracts – EVOH-T	Extracts were negative, passed
Carcinogenicity	Carcinogenicity Evaluation of EVOH and EVOH-T using the <i>rasH2</i> Transgenic Mouse Model	Not carcinogenic

B. CARCINOGENICITY TESTING

Carcinogenicity testing was performed utilizing the *rasH2* transgenic mouse model. The purpose of this study was to evaluate the potential carcinogenicity of Enteryx.

The *rasH2* transgenic mouse model was selected for this study because it offers a test system for the evaluation of carcinogenic potential of implanted biomaterials without the confounding factors related to the existence of foreign body sarcomagenesis (FBS) mechanism in rodents.

The development of transgenic mice carrying a human prototype C-Ha-ras gene (*rasH2* mice) has been recognized as an opportunity to evaluate carcinogenic potential of biomaterials, since rapid carcinogenicity testing of mutagenic and non-mutagenic chemical compounds has been validated in this animal model. In these mice, the foreign body sarcomagenesis response can be differentiated from chemically mediated carcinogenicity within the six-month exposure period to the test article.

In this study, Millipore filters (MF) with a pore size of 0.65 μm and 0.05 μm were implanted as FBS control groups. Urethane, alone and loaded onto Millipore filters, was utilized as the chemical carcinogen control based on a review of the current literature.

Enteryx was administered subcutaneously in 400 mice, with 10 animals from each sex and genotype (transgenic and non-transgenic) assigned to each of the treatment groups.

No differences in body weight gain, terminal mean body weights, or relative tissue weights were observed between animals exposed to the test articles or animals that had implanted Millipore discs. Similarly, no significant histologic findings were observed in any animals exposed to the test articles either at the site of implantation or in any of the 50 tissues that were examined microscopically. No tumors were observed at the site of implantation of the 0.05 μm MF discs, however, an increased level of fibroplasia and decreased level of histiocytic infiltration was observed in these animals. These changes are consistent with early histopathologic alterations, which were found in the literature to be precursors of induction of foreign body sarcomas using small pore (less than 0.10 μm) filters.

In contrast, the cellular character of the test site response observed in animals injected with Enteryx was similar to the response elicited by the 0.65 μm MF discs used as a negative control, establishing the absence of any precursors of induction of foreign body sarcomas. Mice exposed to urethane administered either subcutaneously or on a coated MF disc had a significantly increased incidence of lung and splenic tumors in comparison to their non-transgenic littermates.

In conclusion, the findings of this study establish that Enteryx is non-carcinogenic in the *rasH2* transgenic mouse.

C. LONG-TERM ESOPHAGEAL IMPLANTATION STUDIES

The long-term safety of Enteryx was evaluated in two animal models, canines and Yucatan minipigs. The long-term safety of intramural and extramural LES implants was evaluated in canines and the long-term safety and effect on resting LES pressure was evaluated in minipigs.

1. Canine LES Implant Study

Intramuscular implantation was performed in 16 canines to evaluate the safety of EVOH-T when injected intramurally at the lower esophageal sphincter (LES) and transmurally above and below the LES. An additional study objective was to develop an endoscopic technique of placement of EVOH-T at the gastroesophageal junction, to augment the LES.

Cranial, chest and abdominal x-rays were performed immediately after injection of EVOH-T, and again four weeks post-implantation to assess the location of the EVOH-T, and of any migration. Endoscopy was performed at three days and one month following EVOH-T injection, to assess mucosal and local response to the device material. Hematology was performed for evidence of any signs of systemic toxicity. Of the 16 animals, 13 were intended for short-term evaluation, and were sacrificed at one month, while the three additional dogs were followed for 12 months to evaluate implant stability.

Twelve-month follow up data on three animals showed very minimal or no tissue reaction around major vessels, the trachea, and the right atria. Full body x-ray exams established the absence of migration of the EVOH-T. These study results demonstrate that EVOH-T can be injected safely into the dog with minimal long-term response.

2. Yucatan Minipig LES Implant Study

The long-term safety of EVOH-T was evaluated in 15 Yucatan minipigs to evaluate the dosing and location of EVOH-T, to assess the safety of submucosal or intramuscular LES implants, and in selected animals, to assess LES (lower esophageal sphincter) compliance changes, or yield pressures.

All animals tolerated the implants well and no complications were observed. Histology was performed on animals sacrificed at two weeks, four weeks, five weeks, six weeks, three months, six months, and one year. Over the first month following injection, an inflammatory response consisting predominantly of macrophages was observed, and this response is associated with the production of fibrotic capsule that surrounds the mass of the implanted material. By three months, (and most certainly by six months) post-implantation, the tissue surrounding the implant

sites was quiescent. Mature, well-delineated capsules of varying thickness surrounded the sites, separating them from the esophageal muscle or the interstitial connective tissue.

Pre-injection and post-injection manometric evaluation of the LES area was performed in a subset of animals, to determine overall total LES length, intra-abdominal LES length, and LES pressure. Yield pressure was assessed using both gas insufflation and water infusion to determine the pressures and volumes required to cause the LES to open. When comparing pre-injection and post-injection yield volumes, considerably higher yield volumes were observed post-injection, indicating that the LES was able to withstand much higher pressures before yielding.

D. CONCLUSIONS

In the USP seven-day rabbit muscle implant study, EVOH-T was compared to a negative control (polyethylene implants), and was found to cause a more significant local effect in the muscle tissue. However, this observation was consistent with the course of foreign body reaction observed in the other EVOH-T implantation studies, in which there is an initial tissue reaction, which resolves over time, and is consistent with the extensive body of published data on the host response to the three most commonly implanted biomaterials, i.e., polyethylene terephthalate, expanded polytetrafluoroethylene, and polypropylene.

The results of these extensive in vitro and animal studies support the use of Enteryx for implantation in the lower esophageal sphincter for the treatment of gastroesophageal reflux disease (GERD).

IX. SUMMARY OF CLINICAL STUDIES

A. STUDY OBJECTIVE

A prospective, multicenter clinical study was conducted under IDE G000065. The purpose of the clinical trial was to evaluate the safety and effectiveness of Enteryx as an implantable agent for the treatment of GERD.

B. STUDY DESIGN

This study was designed to evaluate the safety and efficacy of endoscopic implantation of Enteryx for the treatment of GERD. Eighty-five (85) subjects were enrolled at eight sites. The assessment of safety and efficacy of Enteryx was based on results of the twelve-month examination.

1. Effectiveness Parameters

Patients were assessed for a reduction in dose of medication, an improvement in GERD-Health Related Quality of Life (HRQL) and SF-36 scores, a reduction in acid reflux measured by intraesophageal pH monitoring, and LES function assessed by esophageal manometry.

2. Safety Parameters

Subjects were clinically assessed, adverse events were evaluated, and endoscopy results were recorded. The location and quantity of the implant were assessed by x-ray.

C. STUDY PROTOCOL

Patients who were considered capable of comprehending the nature of the study, who were likely to comply with the visit schedule, who provided informed consent, and who conformed to the following inclusion/exclusion criteria were considered for enrollment in the study.

Patients with a previous diagnosis of GERD who were under medical therapy with PPIs (proton pump inhibitors) for at least three months with successful alleviation of GERD symptoms were enrolled into the study.

1. Inclusion Criteria

Patients who met all of the following initial inclusion criteria were eligible for inclusion in the study:

- ?? History of heartburn, regurgitation, or both prior to the initiation of proton pump inhibitor therapy
- ?? Taking daily proton pump inhibitor for at least the last three months
- ?? Responsive to a standard dose of PPI as manifested by a baseline GERD-HRQL symptom score of ? 11
- ?? Surgical candidates in the unlikely event of a complication related to this procedure (ASA I or II)

- ?? At least 18 years of age
- ?? Not pregnant by history or had a negative pregnancy test or surgical sterilization
- ?? Patients who agreed to participate, understood the content of the consent form, and signed the consent form
- ?? Had GERD symptoms that returned upon discontinuing PPI therapy for 10-14 days, as manifested by a GERD-HRQL symptom score of ≥ 20
- ?? A confirmed diagnosis of gastroesophageal reflux disease by prolonged (>12 hour) pH-metry with $\geq 5\%$ of total time $\text{pH} < 4$ OR $\geq 3\%$ of the supine hours $\text{pH} < 4$

2. Exclusion Criteria

Patients with the following conditions were excluded from the study:

- ?? Esophageal motility disorder other than GERD manifested by $\geq 50\%$ nonpropagated primary waves after wet swallows
- ?? Any significant multisystem disease that would compromise their ability to tolerate an endoscopic procedure
- ?? Prior gastric or GERD surgery
- ?? Scleroderma
- ?? Persistent esophagitis \geq Grade III (Savary-Miller)
- ?? Barrett's epithelium
- ?? Hiatus hernia $\geq 3\text{cm}$ by endoscopic evaluation
- ?? Gross obesity (BMI ≥ 35)
- ?? Any autoimmune disorder that required therapy within the last two years
- ?? Suspected or confirmed esophageal or gastric cancer
- ?? Esophageal or gastric varices
- ?? Anticoagulant use, other than 300mg aspirin or equivalent per day
- ?? Patients who were unwilling to participate in all of the follow-up studies

3. Treatment Procedures

All patients were screened for study eligibility. The following information was obtained and testing was performed for all subjects enrolled in the study: a medical history, esophageal manometry, UGI endoscopy, and barium esophagram. Prior to treatment, subjects completed the GERD-specific Health Related Quality of Life (GERD-HRQL) and the SF-36 Health Survey questionnaires. They were asked to first complete the questionnaires based on their current PPI medications. Proton pump inhibitors (PPIs) were then discontinued for at least 10 days, after which subjects completed the questionnaires a second time. In addition, a prolonged (>12 hour) pH study was performed while the subjects were off PPI therapy. Subjective and objective tests

were completed again at the one, three, six and twelve-month treatment follow-up visits, as defined in the event schedule.

D. DESCRIPTION OF STUDY POPULATION AND RESULTS

Of the 85 subjects enrolled in the study and treated with Enteryx, 49 (57.6%) subjects were male and 36 (42.4%) were female. The mean age for the study population was 49.6 years (SD 11.7, range 26.8 - 73.7 years), and the majority of subjects (78%) were over 40 years of age at the time of treatment. The majority of the enrolled subjects were Caucasian (92.9%); 3.5% of subjects were Black; 2.4% were Hispanic, and 1.2% were Asian. The mean body mass index (BMI) was 28.3 (SD 3.97, range 18.5 - 37.4), with the majority of subjects (67.1%) with BMI over 26 but less than 35.

E. EFFECTIVENESS RESULTS

A successful outcome was defined as elimination of all PPI use or a reduction in use of PPIs by at least 50% as compared to baseline usage. Patients who experienced a smaller reduction in use of PPIs, i.e., <50%, who continued to use PPIs at the baseline levels, or who required an increase in PPI usage were considered not improved.

At 12 months, 80.3% of all study subjects (C.I. 69.9% to 88.3%) were able to completely eliminate (70.4%) or reduce = 50% their use of PPIs (9.9%). Since the 95% confidence interval (69.9% to 88.3%) is entirely above the 50% criterion, it can be stated that the primary hypothesis of a statistically significant reduction of PPI utilization was demonstrated (p<0.0001 by the sign test).

PPI USE 12 MONTHS POST-PROCEDURE

	n	% (CI)¹
Medication Improved	65/81	80.3% (69.9 to 88.3%)
Off all PPIs	57	70.4%
Dose reduced ? 50%	8	9.9%
Medication Not Improved	16/81	19.7%
Dose reduced < 50%	1	1.2%
Dose maintained	12	14.8%
Dose increased	3	3.7%

¹ Clopper-Pearson 95% Confidence Interval

The proportion of patients using supplementary non-PPI medications for treatment of GERD was very low for the overall study population. At the 12-month examination 14.8% of subjects (12 subjects) reported use of antacids on an as-needed basis and 3.7% of subjects (3 subjects) used antacids on a daily basis. Only three subjects reported using H₂ antagonists at a frequency of less than daily use. These data suggest that treatment with Enteryx allowed the majority of patients to discontinue use not only of PPIs, but also of other GERD medications, including antacids and H₂ antagonists.

SF-36 HEALTH SURVEY

The SF-36 Health Survey questionnaire, a secondary efficacy measurement, was completed by each study subject at baseline while on PPI treatment, at baseline following withdrawal of PPI treatment for 10-14 days, and at one month, three months, six-months and 12 months following treatment with Enteryx.

Physical Component

SF-36 PCS mean scores at baseline were better for subjects while on PPI therapy than off PPIs. At 12 months following treatment with Enteryx, mean physical component scores were also significantly improved over the mean score at baseline for subjects off PPI therapy (49.4 vs 43.4, $p < 0.001$) and were comparable to scores reported at baseline for subjects while on PPIs.

Mental Component

SF-36 MCS mean scores were *not* significantly different for subjects while on PPI therapy than off PPIs at baseline. At 12 months following treatment with Enteryx, mean scores were not significantly different than subjects either on PPI therapy at baseline (50.0 vs. 51.4, $p = 0.444$) or off PPIs at baseline (50.5 vs. 50.2, $p = 0.160$). Since the change from baseline for SF-36 MCS was not statistically significant by the Wilcoxon signed ranks test, the results were examined for the patients who were improved at 12 months (i.e., PPI use eliminated or reduced = 50%) using the sign test. While a less powerful statistical tool, patients whose medication use improved following Enteryx treatment continued to have statistical significance ($p = 0.026$), suggesting a favorable trend in treatment responders.

Together, these findings suggest that Enteryx is capable of replacing PPIs with no change in SF-36 scores.

	Baseline (on PPIs)		Baseline (off PPIs)		p value
	N	Mean (SD)	N	Mean (SD)	
Quality of life score					
SF-36 MCS	81	51.2 (9.44)	81	48.5 (11.49)	0.077
SF-36 PCS	81	47.8 (9.43)	81	43.1 (10.13)	<0.001
	Baseline (off PPIs)		12 Months post-Treatment		p value
	N	Mean (SD)	N	Mean (SD)	
Quality of life score					
SF-36 MCS	74	50.2 (9.71)	74	50.5 (10.76)	0.160
SF-36 PCS	74	43.4(10.16)	74	49.4 (9.32)	<0.001

VELANOVICH GERD-HRQL SYMPTOM SCORE

The Velanovich GERD-HRQL questionnaire consists of a series of questions related to symptoms experienced by the subject in the last five days. The following scale was used to record the intensity of the symptoms:

- 0 = no symptoms (very satisfied)
- 1 = symptoms noticeable but not bothersome (satisfied)
- 2 = symptoms noticeable and bothersome but not every day (neutral)
- 3 = symptoms bothersome every day (dissatisfied)
- 4 = symptoms affect daily activities (very dissatisfied)
- 5 = symptoms are incapacitating – unable to do daily activities

The questionnaire was completed by each subject at baseline while on PPI treatment, at baseline with PPI therapy withdrawn, and at one month, three months, six months, and twelve months following treatment with Enteryx. Results were reported as the sum of questions related to heartburn scores (sum of questions 1-9) and to sum of questions related to regurgitation scores (sum of questions 10-13).

Sum of Questions 1-9 (Heartburn Score)

The mean severity score for the sum of questions 1-9 was significantly worse at baseline with patients off PPI therapy as compared to baseline on PPI medications (26.4 vs 5.4, $p < 0.001$).

Mean severity score improved significantly following treatment with Enteryx as compared to baseline scores while off PPIs at each follow-up interval ($p < 0.001$). Consistent with the findings for each of the individual questions that are comprised in the summary score, scores following Enteryx treatment were comparable to those observed for patients on PPI therapy at baseline, further confirming that treatment with Enteryx is an effective alternative to chronic use of PPI therapy.

Sum of Questions 10-13 (Regurgitation Score)

The mean regurgitation severity score for the sum of questions 10-13 was significantly worse at baseline with patients off PPI therapy as compared to baseline PPI medications (11.1 vs 2.8, $p < 0.001$). Mean severity scores following Enteryx treatment were significantly improved compared to baseline scores for patients off PPI treatment ($p < 0.001$). Also consistent with the scores for the individual questions, scores for the sum of questions 10-13 were comparable for patients at baseline while on PPIs and following treatment with Enteryx.

	Baseline (on PPIs)		Baseline (off PPIs)		p value
	N	Mean (SD)	N	Mean (SD)	
Symptom score					
GERD-HRQL (Q1-9)	85	5.4 (3.74)	85	26.4 (6.62)	<0.001
GERD-HRQL (Q10-13)	85	2.8 (3.33)	85	11.1 (5.31)	<0.001

	Baseline (off PPIs)		12 Months post-Treatment		p value
	N	Mean (SD)	N	Mean (SD)	
Symptom score					
GERD-HRQL (Q1-9)	77	26.2 (6.67)	77	8.9 (9.70)	<0.001
GERD-HRQL (Q10-13)	77	10.9 (5.40)	77	3.1 (4.22)	<0.001

In conclusion, the GERD-HRQL data indicate that at 12 months following Enteryx treatment, study subjects felt significantly better compared to baseline symptoms off PPIs and had comparable symptom control to baseline scores on PPIs. These data illustrate that the Enteryx procedure can relieve heartburn and regurgitation symptoms and provide an effective alternative to chronic PPI use.

pH-METRY

Subjects underwent prolonged (> 12 hour) pH probe monitoring at baseline off PPI therapy for at least 10 days, and at twelve months following Enteryx treatment. The following data were recorded:

- ?? % total time $\text{pH} \leq 4$
- ?? % upright time $\text{pH} \leq 4$
- ?? % supine time $\text{pH} \leq 4$
- ?? total number of episodes
- ?? longest episode duration (minutes)

Percentage of Time $\text{pH} < 4$

For all subjects with paired data at Month 12, 26/67 (39%) of subjects normalized their pH measurement, as compared to baseline. Further, 43.1% (25/58) of patients who experienced an improvement in PPI use at 12 months also had normalized pH. In contrast, among patients who did not experience an improvement in PPI use at 12 months, only 11.1% (1/9) had normalized pH.

At baseline for the cohort of patients who had baseline and 12 month pH metry performed, the mean percentage of time during testing that pH was < 4 was 14.34% (SD 14.68%). At twelve months following Enteryx treatment, the mean percentage of time at pH < 4 was 9.21% (SD 9%). The mean overall percentage of time at pH < 4 was significantly reduced (improved) at twelve months following Enteryx treatment ($p = 0.002$) compared to baseline off PPIs. These statistically significant reductions in overall time at pH < 4 are indicative of a significant improvement in pH-metry at six and twelve months post-treatment with Enteryx.

Percentage of Upright Time $\text{pH} < 4$

At baseline for the cohort of patients who had baseline and 12 month pH metry performed, the mean percentage of upright time during testing that pH was < 4 was 14.27% (SD 15.35%). At twelve months following Enteryx treatment, the mean percentage of upright time at pH < 4 was 9.92% (SD 10.72%). The mean percentage upright time at pH < 4 was significantly reduced (improved) at twelve months following Enteryx treatment ($p = 0.026$) compared to baseline off PPIs. These statistically significant reductions in upright time at pH <4 are indicative of a significant improvement in pH-metry at six and twelve months post-treatment with Enteryx.

Percentage of Supine Time pH < 4

At baseline for the cohort of patients who had baseline and 12 month pH metry performed, the mean percentage of supine time during testing that pH was < 4 was 12.01% (SD 18.57%). At twelve months following Enteryx treatment, the mean percentage supine time at pH < 4 was 6.97% (SD 12.08%). The mean percentage supine time at pH < 4 was significantly reduced (improved) at twelve months following Enteryx treatment ($p = 0.032$) compared to baseline off PPIs. These statistically significant reductions in supine time at pH<4 are indicative of a significant improvement in pH-metry at six and twelve months post-treatment with Enteryx.

Total Number of Episodes

At baseline for the cohort of patients who had baseline and 12 month pH-metry performed, the mean total number of episodes with pH was < 4 was 162.04 (SD 112.12). At twelve months following Enteryx treatment, the mean total number of episodes with pH < 4 was 114.82 (SD 77.21). The mean total number of episodes with pH < 4 was significantly reduced (improved) at twelve months following Enteryx treatment ($p = 0.002$) compared to baseline off PPIs. These statistically significant reductions in the mean total number of episodes with pH<4 are indicative of a significant improvement in pH-metry at six and twelve months post-treatment with Enteryx.

Longest Episode Duration

The longest recorded episode duration of pH < 4 in study subjects at baseline for the patients with baseline and 12 month data was 33.5 minutes (SD 45.89), while the longest recorded episode duration at 12 months follow-up after treatment with Enteryx, was 21.4 min. (SD 25.54). These results indicate that there was a reduction in the maximum episode duration at the twelve month visit following Enteryx treatment as compared to baseline off PPI treatment, although this difference did not reach statistical significance ($p=0.209$).

Symptom	Baseline (off PPI)		12 Months		p value ²
	n	Mean(SD)	n	Mean (SD)	
pH ? 4 (%) total	67	14.34 (14.68)	67	9.21 (9.00)	0.002
pH ? 4 (%) upright	58	14.27 (15.35)	58	9.92 (10.72)	0.026
pH ? 4 (%) supine	59	12.01 (18.57)	59	6.97 (12.08)	0.032
Episodes (Normalized)	67	162.04 (112.12)	67	114.82 (77.21)	0.002
Longest episode (min)	65	33.5 (45.89)	65	21.4 (25.54)	0.209

MANOMETRY

Subjects underwent manometry before treatment with Enteryx (i.e., within the three months prior to enrollment), six months, and twelve months following Enteryx treatment. Lower esophageal sphincter (LES) pressure and length were recorded, as was peristaltic amplitude and residual LES pressure during relaxation.

Physiologic Method		Baseline	Month 12
LES pressure (mm Hg)	N	69	69
	Mean	14.27	13.10
	Standard deviation	7.03	7.75
	p-value ³		0.651
LES length (cm)	N	59	59
	Mean	2.6	2.8
	Standard deviation	1.04	1.28
	p-value		0.258
Peristaltic amplitude (mm Hg)	N	68	68
	Mean	74.7	79.2
	Standard deviation	30.75	36.82
	p-value		0.502
Residual LESP during relaxation (mm Hg)	N	65	65
	Mean	2.90	2.53
	Standard deviation	5.39	3.84
	p-value		0.577

DeMeester⁵ described the interaction of overall sphincter length and pressure in maintenance of normal sphincter function. The shorter the overall length of the LES, the higher the pressure

² Wilcoxon Signed-Rank

³ Wilcoxon Signed-Rank

must be to maintain sufficient resistance to remain competency. While manometrically measured LES length was significantly longer in the Enteryx group at 6 months, this difference was no longer significant at 12 months by the Wilcoxon signed rank test ($p=0.258$). However, when examining results for the patients who were improved at 12 months (i.e., PPI use eliminated or reduced by at least 50%), the sign test, while a less powerful statistical tool, showed that improved patients continued to have a longer LES measurement ($p = 0.012$), suggesting a favorable trend in treatment responders.

F. SAFETY RESULTS

Adverse events were classified as device related, procedure related, and unrelated to the device or procedure. The severity of adverse events was defined as follows:

- ~~///~~ Mild: causing no limitation of usual activities
- ~~///~~ Moderate: causing some limitation of usual activities
- ~~///~~ Severe: causing inability to carry out usual activities.

This definition of “severe” adverse events was in contrast with the description used in the majority of clinical trials. Customarily, “severe” is used to describe adverse events that may be reportable under 21 CFR 812.150 if they are serious and device related, i.e., lead to death, are potentially life threatening, cause disability or require or prolong hospitalization. In this trial, due to the general good health of the study participants, more conservative definitions were applied. On this basis, “severe” events were defined in terms of disruption of the patient’s daily life. The classification of mild, moderate, or severe was not related to whether medical intervention was necessary.

There were no serious adverse device related events reported during the course of this trial, i.e., there were no events that were potentially life threatening or required surgical intervention.

A total of 122 device-related adverse events were reported for the study population. These adverse events included retrosternal chest pain (78/85 or 91.8%), dysphagia (17/85, or 20.0%), fever (10/85, or 11.8%), belching/burping (6/85, or 7.1%), bloating/flatulence (5/85, or 5.9%), body odor/bad taste (4/85, or 4.7%), and one case each of rib pain and flu syndrome. Of these

adverse events, only five (4%) events were rated as severe at onset, which as noted above, indicated interference with the subject's daily life. The "severe" device-related adverse events consisted of retrosternal chest pain (n=4) and bloating (n=1).

DEVICE-RELATED ADVERSE EVENTS
(85 Patients)

Event	Mild	Moderate	Severe	#	%
Retrosternal Chest Pain	39	35	4	78	91.8%
Dysphagia	10	7	0	17	20.0%
Fever	7	3	0	10	11.8%
Belching/Burping	3	3	0	6	7.1%
Bloating/Flatulence	1	3	1	5	5.9%
Other					
Body Odor/Bad Taste	2	2	0	4	4.7%
Rib Pain	0	1	0	1	1.2%
Flu Syndrome	1	0	0	1	1.2%

A total of 29 (34.1%) adverse events related to the procedure were reported during the course of this study. None of these events were considered to be severe. The events consisted of pharyngitis (n=9), nausea and vomiting (n=7), nausea (n=5), shoulder pain (n=3), dry mouth (n=2), anxiety (n=2), and breast pain (n=1).

SEVERITY OF PROCEDURE-RELATED ADVERSE EVENTS
(85 patients)

Event	Mild	Moderate	Severe	#	%
Sore Throat (Pharyngitis)	8	1	0	9	10.6%
Nausea / Vomiting	3	4	0	7	8.2%
Nausea	3	2	0	5	5.9%
Other					
Shoulder Pain	1	2	0	3	3.5%
Dry mouth	1	1	0	2	2.4%
Anxiety	1	1	0	2	2.4%
Breast Pain	0	1	0	1	1.2%

The procedure related adverse events were anticipated and consistent with what is generally expected during the course of therapeutic endoscopy procedure.

X. CONCLUSIONS

In conclusion, the efficacy of treatment of GERD with endoscopic implantation of Enteryx is demonstrated by the following observations:

?? The primary hypothesis stating that drug use post-Enteryx implantation is less than pre-procedure drug use is fulfilled given the fact that at 12 months, 80.3% of all study subjects were able to completely eliminate (70.4%) use of PPIs or reduce =50% (9.9%) their use of PPIs ($p < 0.0001$, sign test).

Several secondary efficacy endpoints and hypothesis tests underscore the findings regarding the primary efficacy endpoint:

?? The mean Velanovich GERD-HRQL symptom scores for each question and the two summary scores (heartburn and regurgitation) showed significant improvement following treatment with Enteryx as compared to baseline off PPI medications.

?? At all time points following Enteryx treatment, SF-36 Health Survey PCS (physical component) scores were significantly improved over the mean score at baseline for subjects off PPI therapy and were comparable to scores reported at baseline for subjects while on PPIs. SF-36 MCS (mental component) scores demonstrated a significant improvement (sign test) compared to baseline off PPI medications in patients who experienced an improvement in PPI use at 12 months, although SF-36 MCS scores in the overall study population was not significantly different between groups at 12 months. However, at all timepoints following Enteryx treatment, mean mental component scores were comparable to scores reported at baseline for subjects while on PPIs.

?? pH-metry findings were significantly improved following treatment with Enteryx as compared to baseline off PPI medications providing an objective measure of restoration of competency of the lower esophageal sphincter. Further, for those patients who experienced an improvement in PPI use at 12 months, 43.1% had normalized their pH.

?? Manometry findings demonstrated a significant increase in mean LES length (sign test) compared to baseline off PPI medications in patients who experienced an improvement in PPI use at 12 months, although LES length in the overall study population was not significantly different between groups at 12 months. LES length may play an important role in overall competency of the lower esophageal sphincter, as suggested by the relationship between continued improvement in LES length and successful outcome of Enteryx treatment.

Treatment of GERD by endoscopic implantation of Enteryx was shown to be safe in this study, as evidenced by the low incidence, severity, and transient nature of device related adverse events and the complete absence of serious adverse device effects. No mortality was observed in this population.

The data generated in this clinical study establish that endoscopic treatment of GERD by Enteryx implantation offers an alternative to life-long medical therapy and its related costs, non-compliance and intolerance. In addition, the risks associated with endoscopic Enteryx treatment are substantially lower than surgical intervention, with comparable health benefits, a reduced financial burden, and reduction in the loss of productivity associated with standard surgery for management of GERD.

The findings of this study confirm the safety and effectiveness of Enteryx implantation for the treatment of GERD in human subjects.

XI. PANEL RECOMMENDATIONS

XII. CDRH DECISION

XIV. APPROVAL SPECIFICATIONS