SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implant, Intragastric for Morbid Obesity

Device Trade Name: TransPyloric Shuttle/TransPyloric Shuttle Delivery Device

Device Procode: LTI

Applicant's Name and Address: BAROnova, Inc.
1551 Industrial Road
San Carlos, CA 94070

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P180024

Date of FDA Notice of Approval: April 16, 2019

II. INDICATIONS FOR USE

The TransPyloric Shuttle/TransPyloric Shuttle Delivery Device is indicated for weight reduction in adult patients with obesity with a Body Mass Index (BMI) of 35.0-40.0 kg/m^2 or a BMI of 30.0 to 34.9 kg/m^2 with one or more obesity-related comorbid conditions and is intended to be used in conjunction with a diet and behavior modification program.

III. CONTRAINDICATIONS

- Prior surgery or endoscopic intervention that has altered esophageal, gastric, or duodenal anatomy
- Structural abnormality in the esophagus or pharynx such as a stricture or diverticulum that could impede passage of an Overtube and/or an endoscope
- Esophageal abnormality such as erosive esophagitis, eosinophilic esophagitis varices, telangiectasis, or other anomalies that could cause bleeding or other procedural complications
- Patulous gastroesophageal junction
- Known history of structural or functional disorders of the stomach including, gastroparesis, gastric ulcer, gastric mass, chronic gastritis, gastric varices, hiatal hernia (> 4cm), pyloric stricture, or any other disorder of the stomach
- Inflammatory and other pathophysiological conditions of the gastrointestinal (GI) tract, such as Crohn's disease
- Untreated *Helicobacter pylori* infection
- Active gastric or duodenal ulcers
- Continuous therapy with known ulcerogenic medication (e.g., aspirin, NSAIDs)
- Coagulopathy or on anticoagulation or antiplatelet therapy

- Unable or unwilling to take proton pump inhibitors (PPI), or addition of PPI may cause adverse drug interaction with subject's medication or interruption of treatment
- History of portal hypertension, cirrhosis, and/or esophageal varices
- Diagnosis of bulimia nervosa or binge eating disorder or other severe psychiatric disorders
- Pregnancy or planned pregnancy in next 12 months
- Known or suspected allergy to any component materials in the TPS such as silicone, barium sulfate, parylene
- Any other medical condition that would not permit elective endoscopy or anesthesia such as poor general health or history and/or symptoms of severe renal, hepatic, cardiac, and/or pulmonary disease

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the TransPyloric Shuttle/TransPyloric Shuttle Delivery Device labeling.

V. DEVICE DESCRIPTION

The TransPyloric Shuttle (TPS) is a removable intragastric implant intended to facilitate weight loss by self-positioning across the pylorus to create an intermittent obstruction to gastric outflow that delays gastric emptying. The TPS is delivered endoscopically into the stomach and constructed into its functional form using the TPS Delivery Device. Once constructed, the TPS forms a smooth large proximal bulb with a compliant distal tapered region connected to a smaller distal bulb by a flexible silicone tether. The proximal bulb remains within the stomach and the distal bulb is designed to reside either in the stomach or to intermittently cross the pylorus to slow gastric emptying. The TPS resides in the gastric cavity for a treatment period of 12 months. After the 12-month treatment, the TPS is removed by an endoscopic procedure using the BAROnova Retrieval Kit. An illustration of the Transpyloric Shuttle is provided in **Figure 1**.

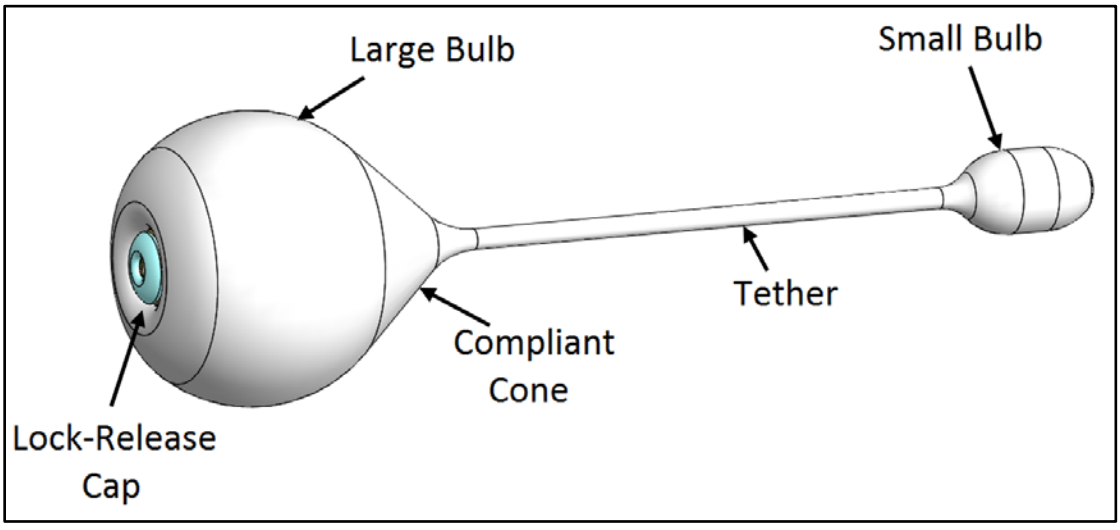

Figure 1. Transpyloric Shuttle (TPS)

The TPS Delivery Device (**Figure 2**) is designed for trans-esophageal delivery of the TPS through the BAROnova Access Sheath. The Delivery Device consists of a distal PTFE shaft preloaded with TPS components, a proximal handle that controls the delivery mechanism, an outer slidable Introducer Sleeve that protects the TPS components during shaft introduction, and an Access Sheath connector that enables secure engagement with the proximal end of the Access Sheath for device positioning. An insufflation port allows for inflation of the TPS skin and insufflation of the gastric cavity during TPS delivery.

The handle on the Delivery Device provides the user interface for actuation of the delivery system mechanisms that control deployment and release of the TPS. The Advance Knob limits the force that can be put into the system, and the progress indicator provides visual feedback on the progress of the TPS coil deployment.

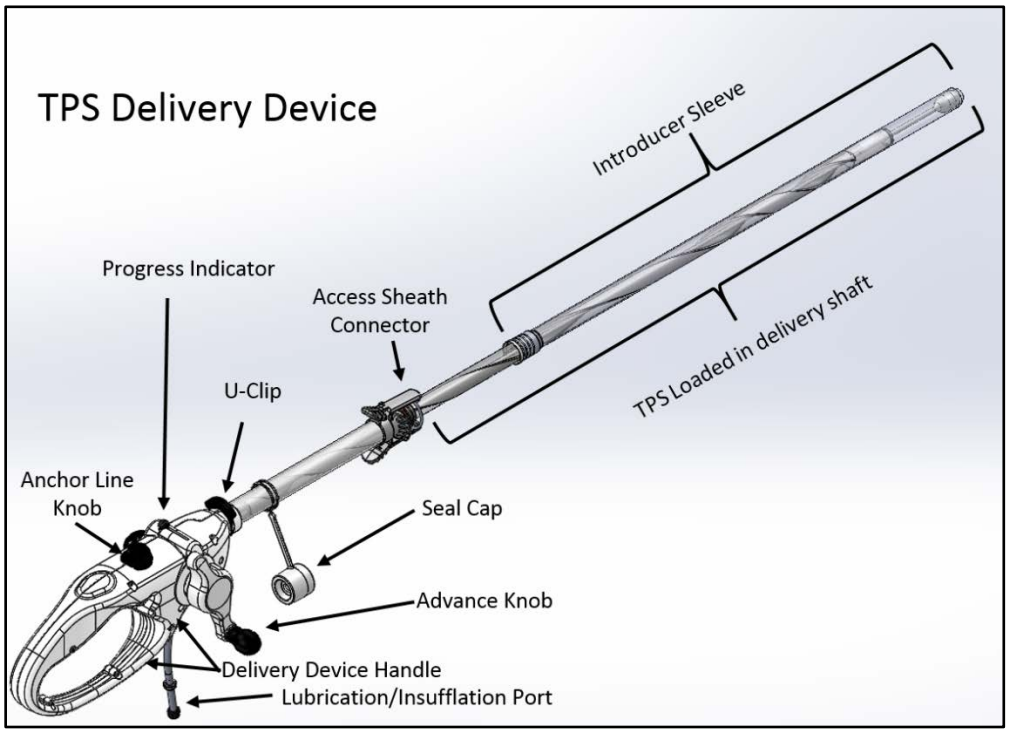

Figure 2. TPS Delivery Device

The TPS Delivery Device consists of the following components, which are packaged and supplied with instructions for use:

- TPS implant pre-loaded in the TPS Delivery Device
- Advance Knob
- Disposable Tube Set
- Introducer Sleeve
- 10 cc Syringe (legally marketed under K170371)

Additional devices and components utilized during the implantation and retrieval procedures include the following:

- BAROnova Access Sheath
- BAROnova Retrieval Kit (legally marketed under K172575)
- Endoscopic forceps (rat tooth) and polypectomy snares
- Insufflation System

The BAROnova Access Sheath is an accessory to the PMA device that was reviewed in a New Accessory Classification Request during PMA review. In parallel with PMA approval, the BAROnova Access Sheath was classified as Class II with special controls under the section 707 accessory provisions of the FDA Reauthorization Act of 2017 (FDARA). This accessory was classified as an Anchored Esophageal Sheath under 21 CFR 876.1510 with a product code of QGG. The BAROnova Access Sheath is used in conjunction with the TransPyloric Shuttle Delivery Device to facilitate insertion and positioning of the device during TPS delivery and deployment (**Figure 3**).

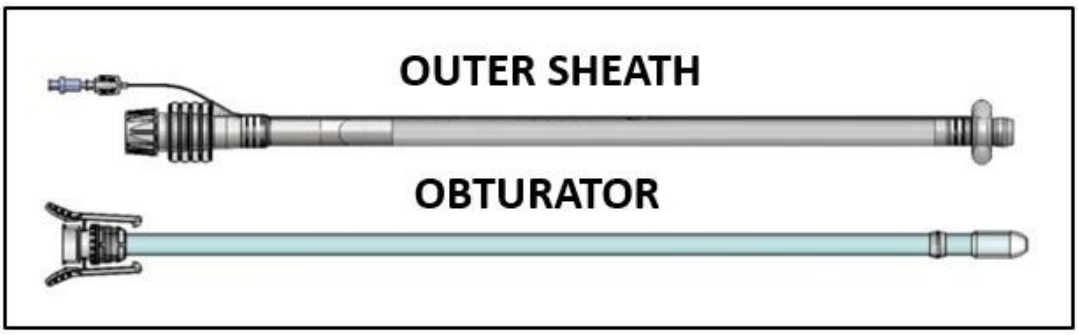

Figure 3. BAROnova Access Sheath

The Obturator is a polymer tube with tapered tip used for atraumatic insertion or repositioning of the Outer Sheath. For use, the Obturator is inserted into, and attached to, the Outer Sheath via a locking handle.

The Access Sheath is compatible with endoscopes with a shaft OD (outer diameter) ranging from 8.8 to 11.0 mm. The Access Sheath is not approved for use with side-viewing or tangentially viewing endoscopes. The BAROnova Access Sheath is designed for single-use, and is disposed after the procedure.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives to achieve weight-loss for individuals with obesity (BMI > 30 kg/m^2), which can be divided into six (6) categories: non-surgical treatments, gastric banding, vagal blocking therapy, gastric emptying therapy, obesity surgery, and intragastric balloons. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his or her physician to select the method that best meets expectations and lifestyle.

Non-Surgical Treatments

Non-surgical treatments for obesity include:

- diet, exercise, and behavioral modifications, and

- prescription weight loss medications.

Gastric Banding
Laparoscopic gastric banding is indicated for patients with a BMI of at least 40 kg/m^2, or a BMI of at least 30 kg/m^2 with one or more obesity-related comorbid conditions, who have failed more conservative weight reduction alternatives.

Vagal Blocking Therapy
Laparoscopic vagal blocking therapy is indicated for use in weight reduction in patients aged 18 years through adulthood who have a BMI of 40 to 45 kg/m^2, or a BMI of 35 to 39.9 kg/m^2 with one or more obesity related co-morbid conditions and have failed at least one supervised weight management program within the past five years.

Gastric Emptying Therapy
Gastric emptying therapy is indicated for weight reduction in patients aged 22 years or older with a BMI of 35-55 kg/m^2 who have failed to achieve and maintain weight loss with non-surgical weight loss therapy. One device is currently available, the AspireAssist. The device allows patients to remove approximately 30% of the food from the stomach at each meal before it is absorbed.

Obesity Surgery
Bariatric surgery is typically recommended for patients with a BMI of at least 40 kg/m^2, or a BMI of at least 35 kg/m^2 with one or more obesity-related comorbid conditions. The most common types of bariatric surgery are described below.

a. Roux-en-Y Gastric Bypass
   In a gastric bypass, the surgeon first constructs a proximal gastric pouch and then creates an outlet from the pouch to a limb of the small bowel. This results in a bypass of most of the stomach and duodenum.

b. Vertical Sleeve Gastrectomy
   Vertical sleeve gastrectomy is a procedure which reduces the size of the stomach by surgical removal of a large portion of the stomach. The open edges are then sutured together to form a sleeve. The size of the stomach is permanently reduced without bypassing the intestines.

c. Biliopancreatic Diversion Duodenal Switch
   The biliopancreatic diversion with duodenal switch is a procedure in which stomach removal is restricted to the outer margin, leaving a stomach sleeve with the pylorus intact. The small intestine is divided with one end attached to the stomach pouch. The majority of the small intestine is bypassed.

Intragastric Balloons
Intragastric balloons are indicated for weight reduction when used in conjunction with diet and exercise in obese patients with a BMI of 30 to 40 kg/m^2 with or without one or more obesity related comorbidities depending on the specific device. Intragastric balloons

are indicated for use in adult patients who have failed weight reduction with diet and exercise alone.

VII. MARKETING HISTORY

The Transpyloric Shuttle/TPS Delivery Device Kit has not been marketed in the United States or any foreign country.

The device has not been withdrawn from any market for any reason relating to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Any patient undergoing the TPS procedure is subject to unforeseen procedural and post-procedural risks (adverse events). Potential risks should be discussed with and understood by the patient prior to TPS placement. It is the responsibility of the physician to provide the patient with this information and to weigh the risk/benefit potential for each patient.

Each patient must be monitored during the entire term of treatment to detect the development of possible adverse events. Each patient should be instructed regarding symptoms of gastrointestinal obstruction, ulceration, and other adverse events which may occur, and should be advised to contact his/her physician immediately upon the onset of such symptoms.

Potential risks associated with an endoscopic procedure and anesthesia include, but are not limited to, adverse reaction to sedation (headache, muscle pain, nausea), anaphylaxis, cardiac arrest, death, hypoxia, infection, myocardial infarction, perforation, pneumonia, and respiratory distress.

Potential risks associated with the TPS include, but are not limited to:

- A feeling of heaviness in the abdomen.
- Abdominal cramps and discomfort from the air used to distend the stomach.
- Allergic reaction to the device's materials (e.g., silicone, barium sulfate, and parylene).
- Alteration of the absorption rate of medications, particularly to enteric-coated medications. Influence on medication dosing, leading to the need to adjust dosing and potential associated complications if dosing is not adjusted, such as hypoglycemia, hypotension, etc.
- Aspiration of gastric contents, aspiration pneumonia.
- Biliopancreatic infection or obstruction, cholecystitis, pancreatitis.
- Cardiac or respiratory arrest during TPS procedures or endoscopy.
- Death.

- Esophageal trauma, perforation, and their related complications.
- Esophageal sphincter and/or pyloric sphincter incompetency associated with sphincter dilation during placement, residence, or removal of the TPS.
- Excess reduction in oral intake, resulting in dehydration or malnutrition.
- Formation of intragastric bezoars.
- Gastroesophageal reflux.
- Gastric stasis and GI symptoms, such as abdominal pain, abdominal spasms, abdominal discomfort, nausea, vomiting, bloating, belching, dyspepsia, dysphagia, heartburn, halitosis, diarrhea or constipation.
- Gastroduodenal obstruction.
- Inability to endoscopically remove part or all of the TPS device, which may result in the need for surgery.
- Influence on digestion of food.
- Insufficient weight loss.
- Interference with abdominal imaging (e.g. CT, X-ray, ultrasound). For MRI, please refer to the MRI safety Information section below.
- Need for medication, endoscopic intervention, early TPS removal, or surgery to treat/correct complications.
- Oropharyngeal trauma, including bleeding, sore or irritated throat, inflammation or infection.
- TPS placement in an improper location such as in the esophagus or duodenum, which results in obstruction, bleeding, or perforation, and their related complications such as pneumothorax.
- Upper GI tract infection or bacterial overgrowth.
- Upper GI tract tissue injury or irritation, resulting in acute or chronic tissue inflammatory response, pain, bleeding, erosion, ulceration, strictures, stenosis, or perforation.

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. **Laboratory Studies**

The integrity and performance of the TransPyloric Shuttle/TransPyloric Shuttle Delivery Device were evaluated with the testing summarized in **Table 1**.

Table 1. Summary of Nonclinical Studies

Test	Purpose	Acceptance Criteria	Results
Nonclinical Performance Testing			
Dimensional and physical testing	Verify the TPS delivery system and TPS implant meet pre-determined dimensional and physical specifications	The fully prepared delivery device must meet the following dimensional and physical requirements: • Insertable Shaft Length: ≥ 24.85” • Delivery Shaft Length with TPS: ≤ 28.63” • Delivery Shaft diameter: ≤ 0.735” • No harsh or sharp features in the patient contacting portion The assembled TPS implant has the following dimensions and physical characteristics: • Proximal bulb diameter: 53-60 mm • Tether length: 10 cm ± 1 cm • Distal bulb diameter: 15-17 mm • TPS density: 1.0 - 1.3 g/ml • External surface of TPS must be smooth, free of any sharp features or gaps ≥ 5mm under 3 psi loading • Materials must not degrade following deployment and/or exposure to the gastric environment The individual TPS implant components have the following dimensions and physical features: • The unwound TPS coil must pass through a diameter of 14.5 mm • TPS Release Cap OD: ≤ 14.35 mm • The empty TPS Skin must collapse to a maximum 22 mm diameter, and provide a smooth tissue-contacting exterior	Pass
Detachment forces	Verify the functionality of detaching the TPS implant from the TPS delivery system during the implant procedure	Following the successful construction of the TPS implant: • Handle removal force: ≤ 5.0 lbf applied at gastroesophageal junction • TPS push off force: < 5.6 lbf	Pass
Simulated use	Verify the functional performance and integrity of the TPS	The TPS delivery system must meet pre-determined functional device criteria to demonstrate:	Pass

	delivery system and TPS implant under simulated use in a representative gastric model	• Successful deployment, locking, and release of an intact TPS under simulated physiological conditions • Full construction of TPS between 9.0 and 11.0 rotations of the Advance Knob • Handle controls must require < 10 lbf force to operate • Tension Lines must be removable with the Advance Knob following deployment • Compatibility with standard endoscope shafts between 8.0 and 11.0 mm • Procedural time less than 45 minutes The TPS implant must meet pre-specified retrieval performance criteria to demonstrate: • Retrieval procedural time must be less than 45 minutes • TPS components must be removable through the BAROnova Retrieval Kit Overtube with ≤ 8 lbf • Empty TPS Skin removal force: ≤ 4.0 lbf using the BAROnova Retrieval Kit	
Insertion and withdrawal force	Verify the TPS delivery system can safely be inserted into and withdrawn from a model representative of patient anatomy	The TPS delivery system must meet the following insertion and withdrawal forces: • Delivery system insertion force ≤ 4.0 lbf • Delivery system withdrawal force ≤ 4.0 lbf	Pass
Implant integrity	Verify the TPS implant and individual components remain intact under the pre-determined loading conditions	The assembled TPS implant must remain intact under the following loading conditions: • The TPS must withstand a 25 lbf off axis load without component failure, permanent deformation, or loss of lock integrity • The TPS must withstand cycled physiologic external pressure exposure without failure of locking elements	Pass

		The individual TPS implant components must meet the following tensile strength requirements: •The Suture Loop must remain secured to the TPS coil proximal loop with ≥ 5.4 lbf •The Weight Cage Cap to Distal Bulb bond strength: ≥ 3.0 lbf •The TPS components (tether, snare to coil and Release Cap) must withstand a 10 lbf tensile load without failure •The TPS skin must allow for 100% elongation without tearing	
Radiographic visibility	Verify the TPS implant features are radiographically visible	The proximal and distal bulb must be radiographically/fluoroscopically visible	Pass
Fluid/Particulate exchange	Verify the pre-determined specifications for fluid and particulate exchange between the gastric environment and the device	The fully constructed TPS implant must meet the following criteria to limit fluid and particulate exchange: • The TPS must have a fluid exchange rate of less than 1 cc/hr with simulated gastric contractions • The TPS must not allow an ingress of particulates 2 mm or greater with simulated gastric contractions	Pass
Implant reliability	Verify the reliability of the implant when subjected to the gastric environment (simulated peristalsis) for a one year period	The fully constructed implant must meet the following reliability criteria: • The proximal bulb must withstand cyclic circumferential loading for a total of 1,730,000 cycles at 3 psi without compromising locking integrity • The locking mechanism must withstand a 400 mmHg pressure applied in a circumferential (equatorial) direction for a total of 100 times without failure of the device locking elements compromising locking integrity • The TPS must withstand loading simulating cyclic pyloric interactions for a total of 1,730,000 cycles at 3 psi • The TPS tether/compliant tapered region must withstand cyclic bending	Pass

		displacement for 433,000 cycles with a load of 3 psi	
Magnetic resonance (MR) compatibility	Assessment of force, torque, heating, and image artifact in a 3T GE Excite MR System to support MR compatibility labeling	• Magnetically induced displacement force based on ASTM F2052 should support labeling • Magnetically induced torque should support labeling • Radio frequency-induced heating should support labeling • Image artifact information based on ASTM F2119-13 should support labeling	Testing results support labeling
Microbiology testing	Determine device total bioburden and assess for specific enteric and pathogenic microbes to confirm acceptable bioburden	Microbial levels should be within established product specifications in coformance with ISO 11737-1:2006/(R)2011, Sterilization of health care products – Microbiological methods – Part 1: Determination of the population of microorganisms on product.	Pass
Packaging Integrity Testing			
Package integrity (simulated distribution and shipping followed by associated package integrity testing)	Validate that packaging materials can withstand the rigors of shipping and distribution and environmental conditions maintaining the product cleanliness	Packaging maintain integrity as demonstrated by the bubble leak testing per ASTM-F2096 and label legibility gross assessment following conditioning and simulated distribution per ASTM-D4332 and ASTM D4169	Pass
6-month Shelf-Life Testing			
Packaging testing	Verify packaging seals meet peel strength requirements to maintain product cleanliness after a minimum of 6 months of shelf-life	Meet requirements per ASTM F88/F88M	Pass
Simulated use, dimensional, physical, Insertion and withdrawal force, and implant	Verify product specifications are met throughout the shelf life	Meet product specifications listed under Nonclinical performance testing	Pass

reliability testing			

B. **Animal Studies**

Evaluations of the TPS implant were conducted in both an acute and chronic animal model to assess the safety and functional use characteristics of the device.

The chronic animal study was conducted in eight (8) juvenile Yucatan mini swine (approximately 25-30 kg) in which a representative version of the TPS was endoscopically deployed and retrieved following an average residence time of 90 (range 84 to 99) days. This study was designed to assess the safety of the TPS implant while in gastric residence by evaluating device performance and integrity, tissue effects throughout, and performing gross pathology after necropsy. In addition, the study also evaluated the ability to successfully deploy and retrieve the device endoscopically. The results analyzed from the eight (8) animals demonstrated device deliverability, durability, and retrievability, with no safety concerns and minimal tissue irritation to the gastric mucosa during residence.

A separate acute animal study was performed with serial deployments and retrievals of six (6) TPS devices in a single live canine to demonstrate that the TPS/TPS Delivery Device meets specified requirements for functionality, safety and compatibility related to acute use of the system in the standard endoscopic procedural environment. This study confirmed an acceptable usability profile of the Delivery Device and implant with no resultant observations of tissue injury.

C. **Additional Studies**

Biocompatibility

The TPS implant is classified as a permanent implant in contact with mucosal membrane during clinical use (> 30 days). In accordance with ISO 10993-1, Biological Evaluation of Medical Devices, the following biocompatibility endpoints were assessed for the TPS implant:

- Cytotoxicity
- Irritation
- Sensitization
- Acute systemic toxicity
- 14-day Subacute systemic toxicity
- Material-mediated pyrogen
- Genotoxicity
- 13-week intramuscular implantation study
- Chemical extractable study
- Toxicological risk assessment of compounds extracted from the device to evaluate chronic systemic toxicity and carcinogenicity

The TPS delivery system is considered to have limited contact with mucosal membrane (< 24 hrs). In accordance with ISO10993-1, Biological Evaluation of Medical Devices, the following biocompatibility endpoints were assessed for the TPS delivery system:

- Cytotoxicity
- Irritation
- Sensitization

Results from the biocompatibility analyses support the biocompatibility of the TransPyloric Shuttle/TransPyloric Shuttle Delivery Device.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study (ENDObesity II study) to establish a reasonable assurance of safety and effectiveness of the TransPyloric Shuttle/TransPyloric Shuttle Delivery Device for weight reduction in patients with obesity: having a Body Mass Index (BMI) of 35-40 kg/m^2, or a BMI of 30-34.9 kg/m^2 with one or more obesity-related comorbid conditions in the US under IDE #G140142. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subject enrollment in the ENDObesity II Trial began in December 2015. The ENDObesity II Study was completed on February 20, 2018, when the last subject exited the study. The database for this PMA reflected data collected through March 23, 2018, and included 524 consented and screened subjects, and 302 enrolled subjects. There were nine (9) investigational sites.

The ENDObesity II study was a multicenter, prospective, pivotal clinical study. The study enrolled subjects into randomized and open-label cohorts. The randomized cohort was a double-blind, concurrent, sham-controlled study with 2:1 allocation to the Treatment (use of the TPS and a moderate intensity lifestyle modification counseling program) or the Control group (sham endoscopic procedure without implantation of the TPS and a moderate intensity lifestyle modification counseling program). A total of 270 subjects (181 TPS and 89 Control) were enrolled in the randomized portion of the study. Upon completion of enrollment into the randomized cohort, 32 additional TPS subjects were enrolled into an Open-Label cohort in which all subjects received the TPS device. All subjects in both cohorts received a low-intensity lifestyle counseling program. The aim of the Open-Label cohort was to verify the success of a manufacturing improvement implemented during the study. Overall, a total of 302 subjects were enrolled in this pivotal study.

The primary objective was to assess the effectiveness of the TPS for weight reduction in the target patient population as compared to sham-control over the 12-month treatment period. The secondary objectives were to assess effectiveness of TPS in changes in weight-related comorbidities, weight-related quality of life, and eating

behavior compared to sham-control patients. The safety objective was to characterize the adverse events occurred in the study.

The randomized treatment groups were compared for percent total body weight loss (%TBWL) at 12 months using a t-test, and for proportion of subjects meeting 12-month %TBWL thresholds (≥ 5%, ≥ 7%, ≥ 10%) using logistic regressions. The randomized groups were compared for repeatedly measured effectiveness endpoints using repeated measurements mixed models, and for proportion of subjects who achieved at least one obesity class reduction (Class I: BMI 30.0-34.9 kg/m^2; Class II: BMI 35.0-40.0 kg/m^2) at 12 months using the Fisher exact test. Analyses on safety were descriptive only. Comparisons between the randomized treatment groups were performed using imputations for missing data.

An ongoing multi-layer safety monitoring process provided evaluation of safety events. This process included the Safety Management Group at Novella Clinical, a Medical Monitor (MM), a blinded Clinical Events Adjudication Committee (CEC), and a Data and Safety Monitoring Board (DSMB).

The control group underwent a sham endoscopic procedure without implantation of the TPS and participated in the same moderate intensity lifestyle modification counseling program that the treatment group participated in.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the ENDObesity II study was limited to patients who met the following inclusion criteria:

   a. Male and female subjects between 22 and 60 years of age
   b. Subjects with a BMI between 30.0-40.0 kg/m^2 inclusive. Those subjects with a BMI of 30.0-34.9 kg/m^2 were required to have one or more obesity-related, mild-moderate comorbidities as follows:
      i. Type 2 Diabetes: meet one of the following criteria and currently not using insulin:
         1. HbA1c of 6.5%-7.5%, or
         2. Controlled, on stable dose of oral medications for at least three months
      ii. Hypertension: meet one of the following criteria:
         1. Arterial blood pressure > 140 mmHg systolic or > 90 mmHg diastolic on or off hypertensive medication
         2. Arterial blood pressure ≤ 140 mmHg systolic and ≤ 90 mmHg diastolic and on hypertensive medication
      iii. Hyperlipidemia: meet at least one of the following criteria:
         1. Fasting total cholesterol level of ≥ 240 mg/dl (6.2 mmol/L)
         2. Fasting total triglyceride level of ≥ 200 mg/dl (2.3 mmol/L)
         3. Low density lipoprotein cholesterol ≥ 160 mg/dl (4.1 mmol/L)
         4. Currently taking lipid-lowering medication based on an elevation of total cholesterol, triglycerides, or LDL

c. History of obesity for at least two years, with history of failure of medically- or commercially-supervised weight loss program
d. History of weight stability (defined as a < 5% change in body weight) for at least three months prior to the screening visit
e. Female subjects of childbearing potential must have a negative urine pregnancy test and must commit to practicing their physician-agreed form of birth control for the duration of participation
f. Willing and able to provide written informed consent
g. Willing and able to comply with study procedures and return for all study visits

Patients were not permitted to enroll in the ENDObesity II study if they met any of the following exclusion criteria:

a. Subjects who were pregnant or planned to become pregnant in next 12 months after enrollment
b. Nursing or pregnancy within the six months prior to enrollment
c. Known hormonal or genetic cause for obesity
d. Prior history of any surgery or endoscopic intervention that has altered esophageal, gastric, or duodenal anatomy, including any bariatric surgery, such as gastric bypass, or restrictive procedures such as laparoscopic adjustable gastric banding
e. Prior treatment with an intragastric balloon for the purpose of weight loss, where the balloon was removed < 12 months prior to the screening visit for this study
f. Chronic use (at least past six months) of medications likely to contribute to weight gain or prevent weight loss (e.g., corticosteroids, lithium, olanzapine, risperidone, clozapine, anticonvulsants, glitazones (e.g., pioglitazone), monoamine oxidase inhibitors)
g. A history of gastric or duodenal ulcers
h. After treatment for Helicobacter pylori, subject that still tested positive for H. pylori
i. A history of severe dyspepsia
j. GI tract motility disorders such as esophageal motility disorders, gastroparesis diabeticorum, or intractable constipation
k. History of inflammatory disease of the GI tract, such as Crohn's disease
l. History of celiac disease
m. History of pancreatitis
n. History of portal hypertension, cirrhosis, and/or varices
o. Diabetes treated with insulin or a significant likelihood of requiring insulin in the next 12 months
p. HbA1c > 7.5%
q. Uncontrolled thyroid and adrenal gland disease
r. Uncontrolled hypertension defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg

s. A history of cardiac arrhythmia, ischemic heart disease, myocardial infarction, or chronic heart failure
t. History of cerebrovascular disease, transient ischemic attack, or stroke
u. Presence of localized or systemic infection
v. Anemia (hemoglobin < 11 g/dL for females and < 12 g/dL for males)
w. History of asthma likely to require systemic steroid therapy during the duration of study participation, or frequent use of rescue inhalers
x. Autoimmune connective tissue disorders, known to be immunocompromised, or at risk of becoming immunocompromised (e.g., HIV positive)
y. A history of malignancy except non-melanoma skin cancer
z. Continuous therapy with known ulcerogenic medication (e.g., aspirin > 100 mg/day, NSAIDs)
aa. On anticoagulation or antiplatelet therapy (e.g., Coumadin, Warfarin, Heparin, Pradaxa, Xarelto, Plavix)
bb. Unwilling to avoid use of any weight loss medication, including over-the counter treatments and/or herbal supplements, during the course of the study, or on prescription medications that can be used for weight loss, even if they are not prescribed for weight loss (e.g., Topiramate, Wellbutrin) and stimulant medications (e.g., for ADHD)
cc. Currently participating in, or unwilling to avoid participation in, any non-study-related organized weight loss program (medical or commercial) during the course of the study
dd. Unable to take a minimum daily dose of omeprazole 40 mg or its equivalent, or where the addition of a PPI may cause an adverse drug interaction with the subject's medication or interruption of treatment
ee. Clinically significant abnormal laboratory values, or an EKG that makes the subject a poor study candidate in the opinion of the Investigator
ff. Inability to walk at least 0.8 kilometers per day (10 minutes of continuous walking)
gg. Planned surgical procedure that could impact the conduct of the study
hh. Started on a prescribed medication regimen within the last three (3) weeks, or whose concomitant medication regimen is expected to change during the course of the study, and where the Investigator determines the medication may affect the study outcome
ii. Known allergy to any component materials in the TPS such as silicone, barium sulfate, and parylene
jj. Current smoker or user of nicotine product, or smoking cessation within one year of the screening date
kk. Current abuse of drugs or alcohol, or past treatment for substance abuse
ll. Presence of any severe, uncontrolled psychiatric illness
mm. Inpatient psychiatric treatment within the past year
nn. A score of ≥ 10 on the Patient Health Questionnaire 9 (PHQ-9), indicating moderate depression
oo. Diagnosis of bulimia nervosa or binge eating disorder

pp. Any medical condition (including psychiatric illness) that would interfere with the interpretation of the study results, the conduct of the study, or would not be in the best interest of the subject in the opinion of the site Primary Investigator
qq. Participation in another clinical study within 60 days of the screening date, in a previous or ongoing clinical study, or planning to participate in another clinical study at any time during this study
rr. Employee or family member of BAROnova, the Investigator, or site study staff
ss. The Investigator judges the candidate unsuitable for the study
tt. Has any of the following endoscopic exclusion criteria: esophageal stricture, Barrett's esophagus, erosive esophagitis, varices, angioectasias, gastric mass, antral or peri-pyloric polyps, peptic ulceration, hiatal hernia ≥ 4 cm, pyloric stricture, or any other abnormalities/characteristics that in the opinion of the endoscopist would preclude safe use of the TPS

2. Follow-up Schedule

Subjects were followed for 12 months or until study exit. All subjects were scheduled to return for follow-up examinations at 1 Week and 1, 2, 4, 6, 9, and 12 months, where subjects received physical exams, weight assessment, laboratory testing, and completed validated obesity-specific outcomes questionnaires. At each follow-up visit, subjects were provided standardized lifestyle-modification counseling. In addition, at months 7, 8, 10, and 11 a brief telephone contact was carried out to assist compliance. Initially, endoscopic surveillance at the 2- and 6-month follow-up visits was performed to monitor for possible ulcer occurrence. Following DSMB recommendation based upon low observed ulcer incidence, the routine endoscopic surveillance was discontinued on December 21, 2016. Clinical laboratory blood tests were performed by the clinical laboratory at each investigational site.

The objective parameters measured during the study included weight, BMI, waist and hip circumference measurements, vital signs, concomitant medications, laboratory values, quality of life (using Impact of Weight on Quality of Life (IWQOL-Lite)), and eating behaviors (using Eating Inventory (EI)) and Control of Eating Questionnaires (CoEQ). Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, a review was completed of reported adverse events and, serious adverse events, as well as device- and procedure-relatedness of the adverse events. There was no pre-specified safety endpoint for the study.

With regards to effectiveness, the ENDObesity II Pivotal Study had two (2) co-primary effectiveness endpoints:

- Mean percent total body weight loss (%TBWL) between the Treatment and the Control group at 12 months after the index procedure.

- The proportion of subjects in the Treatment group who achieve ≥ 5 %TBWL at 12 months after the index procedure.

With regard to success/failure criteria, the study hypothesis for the first co-primary endpoint was that the TPS subjects would have superior %TBWL compared to the Control group subjects at 12-month follow-up. The first co-primary endpoint was evaluated using mixed models on multiply imputed samples. If a one-sided p-value was < 0.025, the null hypothesis was rejected.

The study hypothesis for the second co-primary endpoint was that the proportion of subjects in the TPS group with ≥ 5% TBWL ("responders") at 12-month follow-up would be at least 50%. The second co-primary endpoint was evaluated as a Wilson's midpoint estimate and its 95% confidence interval on multiply imputed samples.

For the primary analysis of the co-primary effectiveness endpoints, missing weight values were imputed using the multiple imputation technique. The implementation of imputation was different between subjects who exited the study for medical reasons and other subjects. For subjects who exited the study for medical reasons, missing weight values were imputed using the last-value-carry-forward approach. For other subjects, missing weight values were imputed based on age, sex, study arm, and all available weight values from scheduled follow-ups. Ten imputed samples were created for each analysis.

The effectiveness endpoints were evaluated based on the Per-Protocol (PP) population defined as subjects who received the assigned treatment and did not have any major eligibility violations in the randomized cohort. Both null hypotheses had to be rejected to declare study success.

There were no formal secondary effectiveness endpoints for the ENDObesity II study. The observational analyses included percent excess weight loss (%EWL); BMI reduction; proportion of subjects who achieved at least one obesity class reduction; changes in cardiometabolic risk factors including blood pressure, waist circumference, fasting blood glucose, insulin, insulin-resistance, and lipid profile; changes in quality of life scores, eating behavior and satiety.

B. **Accountability of PMA Cohort**

A total of 524 consented subjects were screened, and 302 subjects were enrolled in the study. Of the 302 enrolled, 270 were in the randomized cohort (181 in the TPS and 89 in Control group) and 32 were enrolled in the Open-Label cohort.

The TPS deployment was unsuccessful in 10 subjects in the randomized TPS group, resulting in 171 subjects in the randomized cohort who received the TPS implant. All

subjects in the Control group and the Open-Label cohort received the intended treatment. In total, 203 subjects successfully received the TPS implant (171 in the randomized cohort and 32 in the Open-Label cohort).

The per-protocol (PP) populations for the randomized cohort included 168 subjects in the TPS group and 89 in the Control group. Among them, 37/168 and 10/89 subjects were withdrawn prior to 12 months and 131/168 and 79/89 completed the 12-month follow up in the TPS and Control groups, respectively.

In the Open-Label cohort, all 32 subjects received the TPS implant; 7/32 withdrew prior to 12-months and 25/32 completed the 12-month follow up.

Figure 4 shows the study accountability tree (ITT = intent-to-treat, ePP = expanded Per-Protocol)

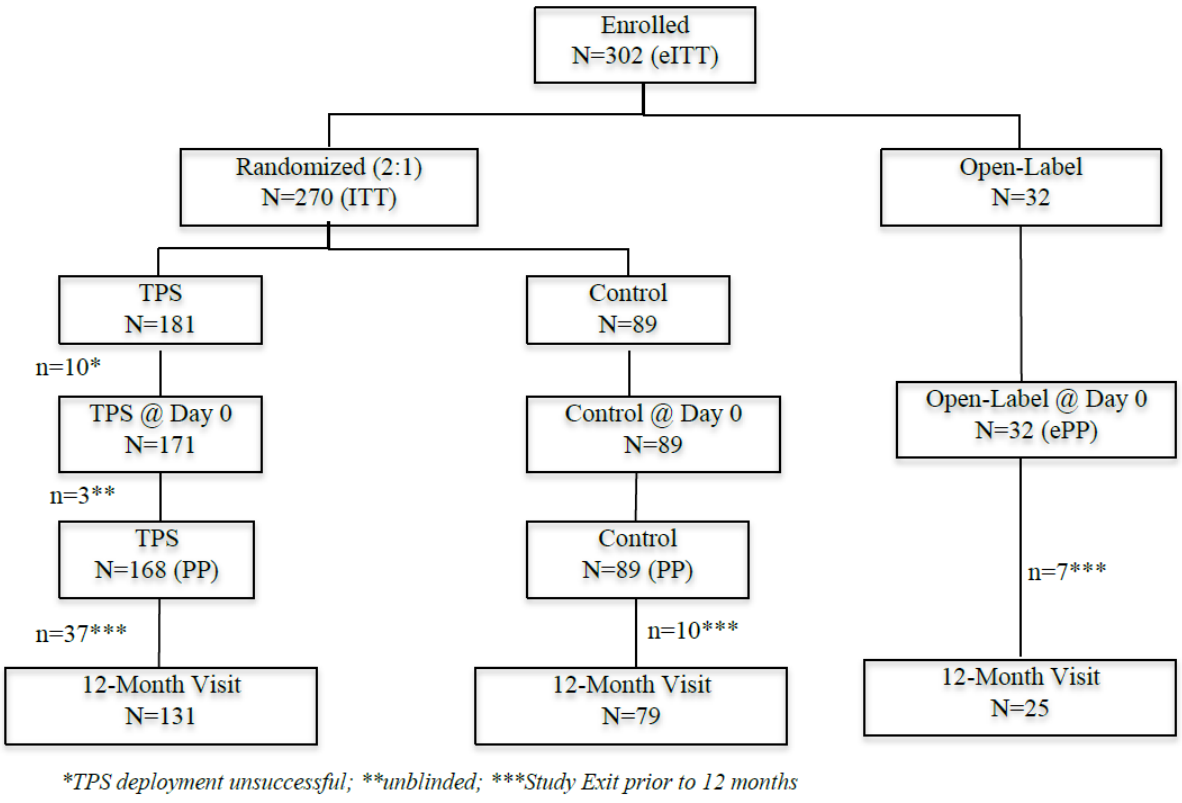

Figure 4. Subject Accountability Flow Chart

Though 44 TPS treated subjects had the device removed and exited the study prior to 12 months (the planned device removal date), 46 subjects in total had the device removed prior to the 12-month planned removal.

C. **Study Population Demographics and Baseline Parameters**

Subjects had a mean age of approximately 43 years, mean weight of approximately 100 kg, and a mean BMI of approximately 36.5 kg/m^2. Approximately 77.5% of subjects had a family history of obesity, almost all had attempted diet and exercise, and 55.4% had attempted weight loss medications previously.

Baseline demographics were similar between the TPS randomized and the Control groups. Females accounted for 93.4% of the subjects in the randomized cohort and 84.4% of the subjects in the Open-Label cohort. Black or African Americans made up 17.7% of subjects in the TPS group and 14.6% in the Control group. The majority of subjects in all groups had Class II obesity. Randomized treatment groups were comparable at baseline with respect to demographics and baseline factors.

Key demographics and baseline physical characteristics are presented in **Table 2**.

Table 2. Baseline Sex, Ethnicity, Race, and Medical History

Parameter Mean (SD)	Randomized TPS (n=181)	Control (n=89)	Open-label TPS (n=32)
Age, Mean (SD)	43.0 (8.9)	43.9 (8.5)	41.9 (8.9)
Sex (female), N (%)	169 (93.4%)	83 (93.3%)	27 (84.4%)
Height (cm), Mean (SD)	165.8 (7.8)	164.7 (7.3)	165.6 (7.3)
Body Weight (kg), Mean (SD)	101.5 (11.9)	98.1 (10.9)	98.9 (12.4)
BMI (kg/m^2), Mean (SD)	36.8 (2.2)	36.1 (2.4)	36.0 (2.6)
Waist Circumference (cm), Mean (SD)	108.1 (9.7)	105.9 (8.5)	108.7 (10.7)
Ethnicity (Hispanic/Latino), N (%)	28 (15.5%)	12 (13.5%)	7 (21.9%)
Race, N (%)			
White	131 (72.4%)	65 (73.0%)	26 (81.3%)
Black/African American	32 (17.7%)	13 (14.6%)	5 (15.6%)
Asian	1 (0.6%)	0 (0.0%)	0 (0.0%)
American Indian/Alaska Native	1 (0.6%)	0 (0.0%)	0 (0.0%)
Native Hawaiian/Other Pacific Islander	1 (0.6%)	1 (1.1%)	0 (0.0%)
Hispanic or Latino	13 (7.2%)	6 (6.7%)	1 (3.1%)
Other	2 (1.1%)	4 (4.5%)	0 (0.0%)
Subjects with Comorbid Conditions, N (%)			
Diabetes	11 (6.1%)	5 (5.6%)	0 (0.0%)
Hypertension	46 (25.4%)	26 (29.2%)	14 (43.8%)
Hyperlipidemia	39 (21.6%)	21 (23.6%)	7 (21.9%)
≥ 1 Comorbid Conditions	117 (64.6%)	63 (70.8%)	20 (62.5%)
≥ 2 Comorbid Conditions	42 (23.2%)	20 (22.5%)	7 (21.9%)

D. **Safety and Effectiveness Results**

1. Safety Results

The endoscopic placement procedure for the TPS was attempted in 213 subjects (181 in the randomized cohort and 32 in the Open-Label cohort), and the TPS was successfully placed in 203 subjects (171 in the randomized cohort and 32 in the Open-Label cohort). The safety assessment of the TPS included a complete review of reported serious adverse events (SAEs) and adverse events (AEs), as well as device and procedure-relatedness of adverse events. The device-related safety assessment included the 203 subjects who received the TPS. . Procedure-related assessments included the 213 subjects in whom the TPS deployment was attempted and the 89 subjects in the Control group. The key safety outcomes and adverse effects are reported in **Table 3**, **Table 4**, **Table 5**, **Table 6**, and **Table 7**.

Adverse effects that occurred in the PMA clinical study:

a. Serious Adverse Events

There were no deaths or unanticipated serious adverse device effects in the study. There were nine (9) device- or procedure-related serious adverse events (SAEs) in six (6) treated subjects. The observed device- or procedure-related SAEs included one esophageal rupture (with an associated pneumothorax) that occurred during an unsuccessful delivery attempt; and seven (7) SAEs related to TPS in residence, which resolved following TPS removal. The overall incidence of device- or procedure-related SAEs was 2.82% in all subjects in whom the TPS procedure was attempted (6/213, 95% C.I. 1.30%, 6.01%) (**Table 3**). Among subjects who received the TPS device, the most common SAE was device impaction that occurred in 1.97% (4/203).

Table 3. Device- or Procedure-Related Serious Adverse Events[1]

SAEs by MedDRA Categorization	# of Events	Subjects % (n/N)	Time to Onset (Days)	Device Removed Due to SAE
Esophageal rupture*	1	0.47% (1/213)	0	NA
Pneumothorax*	1	0.47% (1/213)	0	NA
Upper abdominal pain	1	0.49% (1/203)	2	Yes
Gastric ulcer**	1	0.49% (1/203)	119	Yes
Vomiting**	1	0.49% (1/203)	189	Yes
Device impaction**	4	1.97% (4/203)	Mean (SD): 195 (95) Range: 119-261	Yes

**Pneumothorax was due to the esophageal rupture, which occurred in the same subject.*

***Overlapping events. Device impaction included the patient with gastric ulcer (1) and the patient with vomiting (1)*

[1] *A serious adverse event is an adverse event that*

- *Led to a death*
- *Led to a serious deterioration in health resulting in*

- *a life- threatening illness or injury*
- *a permanent impairment of a body structure or body function*
- *in-patient hospitalization (> 24 hours) or prolongation of an existing hospitalization*
- *required medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment of a body structure or body function*

- *Led to fetal distress, fetal death, or a congenital abnormality or birth defect*

To improve the TPS deployment success rate, a minor manufacturing modification was implemented during the study. After the modification, the TPS deployment success rate was increased to 99.1% (105/106) compared to a pre-modification success rate of 91.6% (98/107).

b. Adverse Events

The most commonly reported device-related adverse events were gastrointestinal events, most commonly nausea, upper abdominal pain, vomiting, and dyspepsia, with the majority mild to moderate in severity. Almost all (99.0%) of TPS subjects had at least one device-related AEs during the study (**Table 4**). The incidence of procedure-related events was similar in both groups (63.9% vs. 62.9% in TPS and Control groups, respective); most commonly oropharyngeal pain associated with the procedure.

Table 4 summarizes the device- and procedure-related adverse events that occurred in ≥ 10% of TPS subjects.

Table 4. Summary of Device and Procedure Related Adverse Events Reported in ≥ 10% of Subjects (Safety Population)

MedDRAPreferred Term	Device Related	Procedure Related	
	TPS (n=203)	TPS (n=213)	Control (n=89)
Subjects with Any Events	201 (99.0%)	136 (63.9%)	56 (62.9%)
Subjects with Gastrointestinal Events	200 (98.5%)	87 (40.9%)	23 (25.8%)
nausea	128 (63.1%)	41 (19.3%)	7 (7.9%)
abdominal pain upper	127 (62.6%)	30 (14.1%)	10 (11.2%)
vomiting	118 (58.1%)	22 (10.3%)	3 (3.4%)
dyspepsia	111 (54.7%)	22 (10.3%)	4 (4.5%)
diarrhea	77 (37.9%)	4 (1.9%)	1 (1.1%)
abdominal distension	75 (36.9%)	18 (8.5%)	0 (0.0%)
gastroesophageal reflux	70 (34.5%)	8 (3.8%)	0 (0.0%)
eructation	67 (33.0%)	12 (5.6%)	1 (1.1%)
gastritis erosive	27 (13.3%)	2 (0.9%)	0 (0.0%)

MedDRAPreferred Term	Device Related	Procedure Related	
	TPS (n=203)	TPS (n=213)	Control (n=89)
gastric mucosa erythema	23 (11.3%)	1 (0.5%)	0 (0.0%)
gastric ulcer	21 (10.3%)	0 (0.0%)	0 (0.0%)
oropharyngeal pain	25 (12.3%)	76 (35.7%)	38 (42.7%)

The commonly reported GI symptoms were rated as mild or moderate in severity 84 to 100% of the time. A summary of the severity and timing of the common GI symptoms is shown in **Table 5**. The median time to onset of these common GI symptoms was 1-2 months (15-74 days) with a median duration for all symptoms but eructation of 3-17 days. Mild eructation had a median duration of 73 days.

Table 5. Summary of Onset and Duration of Device-Related GI Events occurring in ≥ 10% of TPS Subjects (Safety Population)

MedDRA Preferred Term	TPS Subjects (N=203)	# Events	Event Severity Rating			Days to Onset Median, Mean and Range		Median Duration (Days)	Subjects with Event Onset ≤ 3 Days n/N (%)
			Mild # Events (%)	Mod. # Events (%)	Severe # Events (%)				
Nausea	128 (63.1%)	243	133 (54.7%)	93 (38.3%)	17 (7.0%)	Median: Mean: Range:	29.0 82.8 0-355	3.0	89/128 (69.5%)
Abdominal pain upper	127 (62.6%)	221	112 (50.7%)	86 (38.9%)	23 (10.4%)	Median: Mean: Range:	17.0 66.2 0-349	5.0	88/127 (69.3%)
Vomiting	118 (58.1%)	252	138 (54.8%)	92 (36.5%)	22 (8.7%)	Median: Mean: Range:	74.0 105.1 0-376	2.0	54/118 (45.8%)
Dyspepsia	111 (54.7%)	174	83 (47.7%)	65 (37.4%)	26 (14.9%)	Median: Mean: Range:	15.5 59.5 0-363	13.0	67/111 (60.4%)
Diarrhea	77 (37.9%)	126	59 (46.8%)	47 (37.3%)	20 (15.9%)	Median: Mean: Range:	52.0 86.5 0-350	3.5	22/77 (28.6%)
Abdominal distension	75 (37.0%)	110	83 (75.5%)	23 (20.9%)	4 (3.6%)	Median: Mean: Range:	33.0 67.4 0-327	7.0	24/75 (32.0%)
Gastro-esophageal reflux	70 (34.5%)	97	56 (57.7%)	31 (32.0%)	10 (10.3%)	Median: Mean: Range:	42.0 82.6 0-363	12.0	25/70 (35.7%)
Eructation	67 (33.0%)	81	68 (84.0%)	13 (16.0%)	0 (0.0%)	Median: Mean: Range:	27.0 77.8 0-324	73.0	20/67 (29.9%)
Gastritis erosive	27 (13.3%)	36	30 (83.3%)	6 (16.7%)	0 (0.0%)	Median: Mean: Range:	196.0 231.8 46-398	147.5	1/27 (3.7%)

MedDRA Preferred Term	TPS Subjects (N=203)	# Events	Event Severity Rating			Days to Onset Median, Mean and Range		Median Duration (Days)	Subjects with Event Onset ≤ 3 Days n/N (%)
			Mild # Events (%)	Mod. # Events (%)	Severe # Events (%)				
Gastric mucosa erythema	23 (11.3%)	26	20 (76.9%)	6 (23.1%)	0 (0.0%)	Median: Mean: Range:	70.0 130.4 46-356	138.0	0/23 (0.0%)
Gastric ulcer	21 (10.3%)	23	11 (47.8%)	9 (39.1%)	3 (13.0%)	Median: Mean: Range:	273.0 270.7 119-373	68.0	0/21 (0.0%)

Gastroduodenal ulcers were observed in 10.3% (21/203) of TPS subjects at a mean time of 271 days (range 121 to 374 days). A total of 25 ulcers were observed in the study, which were reported in 23 adverse events. There were no ulcer bleeding or perforation complications. Ulcers were asymptomatic or with symptoms overlapping with symptoms of delayed gastric emptying. The ulcers responded to medical management and healing was achieved in a mean time of 73 days (range 56-117 days) after TPS retrieval. **Table 6** summarizes endoscopic ulcer observations.

Table 6. Summary of Endoscopic Ulcer Observations

Ulcer Observations	TPS (n=203)
Subjects with ≥ 1 Ulcer, n (%)	21 (10.3%)
Days to Endoscopic Observation of Ulcer Mean (SD) (Range)	271.2 (83.8) (121, 374)
Ulcer Location, n/N (%)	
Pre-pyloric	13/25 (52%)
Antrum	7/25 (28%)
Pyloric Channel	3/25 (12%)
Gastric body	1/25 (4%)
Proximal Duodenum	1/25 (4%)

Esophageal mucosal injuries occurred in 30 subjects with a similar frequency in TPS and Control subjects; 9.9% (21/213) and 10.1% (9/89) respectively**,** related to the passage of the Access Sheath or Overtube, and to a lesser extent the endoscope.

Forty-six (46/203, 22.7%) subjects who received the TPS device exited the study and had their TPS retrieved prior to 12-month follow-up. Of these, 22/203 (10.8%) exited at or prior to 180 days and 24/203 (11.8%) exited after 180 days. Five (5) of these subjects exited due to a device-related SAE, 1 due to an SAE unrelated to device, 24 due to non-serious adverse events and 16 due to other

reasons not associated with adverse events (**Table 7)**. Overall, the adverse event associated early exit rate was 14.8% (30/203).

Table 7. Summary of Adverse Events Associated with TPS Residence Time < 12 Months

MedDRA Preferred Term	# of Subjects with SAE	# of Subjects with AE	TPS (N=203) N (%)
Abdominal discomfort	0	1	1 (0.5%)
Abdominal pain upper	1	5	6 (3.0%)
Device impaction	4*	3	7 (3.4%)
Diarrhea	0	1	1 (0.5%)
Dyspepsia	0	1	1 (0.5%)
Dysphagia	0	1	1 (0.5%)
Fatigue	0	1	1 (0.5%)
Gastric ulcer	1*	0	1 (0.5%)
Gastroenteritis	0	1	1 (0.5%)
Nausea	0	3	3 (1.5%)
Vomiting	1*	7	8 (3.9%)
Meningioma**	1	0	1 (1.5%)

**Overlapping events. Device impaction included the patient with gastric ulcer (1) and the patient with vomiting (1)*

***Unrelated to device or procedure.*

2. Effectiveness Results

The analysis of effectiveness was based on the 168 evaluable patients PP population at the 12-month time point. The PP population is defined as subjects who received the assigned treatment and did not have any major eligibility violations in the randomized cohort.

Primary Effectiveness Endpoints

Both co-primary endpoints were met:

- The mean percent total body weight loss (% TBWL) was 9.5% for the TPS Group compared to 2.8% in the Control Group ($p < 0.0001$). The TPS group had an average of 6.7% (95% C.I. 4.5 to 8.8) greater %TBWL than the Control group (**Table 8**).

Table 8. %TBWL at 12 Months – PP Population

%TBWL$_{12M}$	TPS (N=168)	Control (N=89)	Difference TPS-Control	p-value
LS* Mean (SE) **95% C.I.**	9.5 (0.7) 8.2 to 10.8	2.8 (0.9) 1.1 to 4.5	6.7 (1.1) 4.5 to 8.8	< 0.0001

**Least Squares mean*

- At the 12-Month follow-up visit, the proportion of TPS subjects who achieved ≥ 5%TBL was 66.8% (95% CI: 59.3 to 74.3) (**Table 9**).

Table 9. Proportion of Subjects in the TPS Group Achieving ≥ 5% TBWL

	TPS (n=168)	p-value*
Proportion of subjects with ≥ 5% TBWL at 12-Months **95% C.I.**	66.8% 59.3 to 74.3	< 0.0001

** p-value for the hypothesis that the proportion is equal to 0.5.*

The percent total body weight loss for the TPS and the Control groups over time is shown in **Figure 5** and **Table 10**. The TPS treatment resulted in continued weight loss throughout 12 months, with the maximum weight loss achieved at Month 12. In comparison, subjects in the Control Group lost the majority of the weight in the first two (2) months after the index procedure. The weight loss between 2 and 6 months in the Control group was marginal. Between 6 and 12 months, the subjects in the Control group regained a portion of the lost weight.

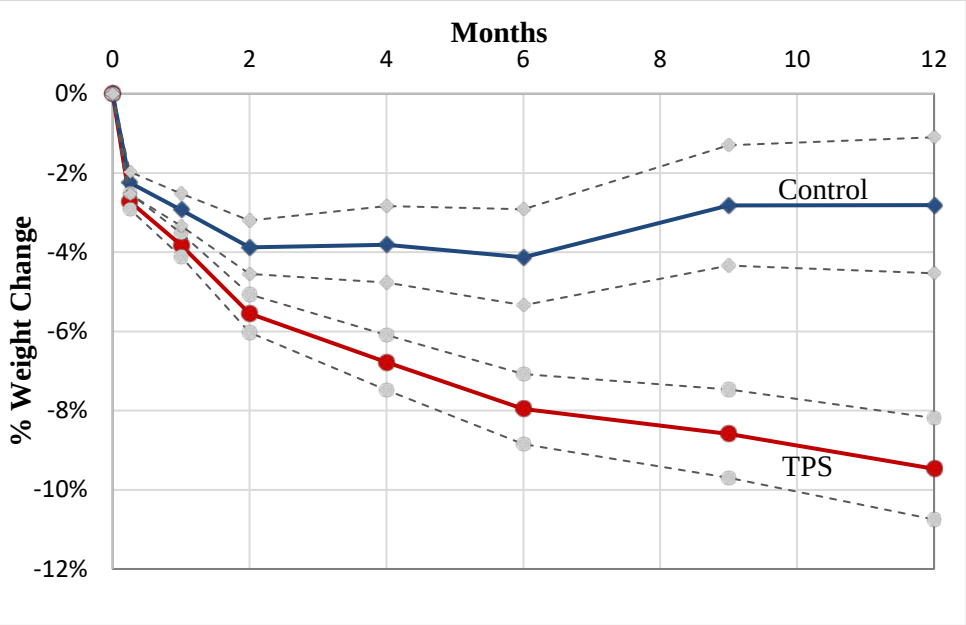

Figure 5. TPS and Control Group Weight Loss Over Time (PP Population)
(Solid lines are mean % weight change, and the dotted lines represent the 95% confidence interval for the means)

Table 10. Summary of %TBWL (SE) by Follow-up Visit, Treatment Group and Analysis Population

	PP Population		mITT Population		ITT Population	
Visit	**TPS (n=168)**	**Control (n=89)**	**TPS (n=171)**	**Control (n=89)**	**TPS (n=181)**	**Control (n=89)**
Week 1	2.72 (0.10)	2.25 (0.14)	2.79 (0.11)	2.21 (0.15)	2.77 (0.10)	2.22 (0.15)
Month 1	3.82 (0.15)	2.93 (0.21)	3.89 (0.16)	2.89 (0.22)	3.86 (0.15)	2.89 (0.22)
Month 2	5.55 (0.25)	3.88 (0.34)	5.63 (0.25)	3.85 (0.35)	5.58 (0.25)	3.86 (0.36)
Month 4	6.78 (0.36)	3.81 (0.49)	6.84 (0.37)	3.80 (0.51)	6.77 (0.37)	3.81 (0.51)
Month 6	7.96 (0.45)	4.13 (0.62)	8.02 (0.45)	4.10 (0.62)	7.94 (0.45)	4.11 (0.63)
Month 9	8.59 (0.57)	2.82 (0.77)	8.62 (0.56)	2.85 (0.77)	8.47 (0.56)	2.86 (0.78)
Month 12	9.47 (0.65)	2.81 (0.87)	9.38 (0.67)	2.95 (0.90)	9.17 (0.66)	2.96 (0.90)

Sensitivity analyses were performed for co-primary endpoints using the ITT, Modified Intent-to-Treat (mITT; excludes 10 implant failures in TPS group), Completed Cases (enrolled subjects who (i) had the 12-month follow-up visit, or (ii) had completed the study based on reaching the BMI objective of ≤ 22.0 kg/m^2 in two consecutive follow-up visits) and other analysis populations as well as different imputation methods. All sensitivity analyses resulted in meeting the pre-determined statistical success criteria for effectiveness. The only exception was the worst-case scenario analysis using the back-to-baseline sensitivity approach

for the second co-primary endpoint. The sensitivity analysis in the mITT population which included all subjects who were randomized and received the assigned treatment, is presented in **Table 11** and **Table 12**.

Table 11. %TBWL at 12 Months (mITT Population)

%TBWL$_{12M}$	**TPS (N=171)**	**Control (N=89)**	**Difference TPS-Control**	**p-value**
LS* Means (SE) 95% C.I.	9.3 (0.6) 8.1 to 10.6	2.8 (0.9) 1.1 to 4.5	6.5 (1.1) 4.4 to 8.7	< 0.0001

**Least Squares mean*

Table 12. Proportion of Subjects in the TPS Group Achieving ≥ 5%TBWL (mITT Population)

	TPS (N= 171)	**p-value**
Proportion of subjects with ≥ 5% TBWL at 12-Months 95% C.I.	66.1% 58.7% to 73.5%	< 0.0001

Secondary Effectiveness Endpoints

Responder Rate

Responder rates for different threshold levels of weight loss are presented in **Table 13.** More than two-thirds of TPS subjects lost at least 5% total body weight compared to less than one-third of subjects in the Control Group. Approximately 40% of subjects in the TPS group achieved at least 10%TBWL.

Table 13. Responder Rates at 12-Month Follow-up Visit by Group

	PP Population % subjects 95% C.I.		**mITT Population** % subjects 95% C.I.	
Parameter	**TPS (n=168)**	**Control (n=89)**	**TPS (n=171)**	**Control (n=89)**
≥ 5% TBWL	66.8% 59.3% to 74.3%	29.3% 19.3% to 39.4%	66.0% 58.5% to 73.6%	30.0% 19.7% to 40.3%
≥ 7% TBWL	53.6% 45.8% to 61.5%	24.8% 15.4% to 34.2%	52.8% 44.7% to 60.8%	25.7% 16.2% to 35.2%
≥ 10% TBWL	39.7% 31.8% to 47.6%	14.0% 6.2% to 21.9%	38.7% 31.2% to 46.2%	14.2% 6.6% to 21.7%

Excess Weight Loss (EWL), Weight Loss, BMI, and Obesity Class Changes

Table 14 summarizes percent excess weight loss, weight loss in pounds, BMI, and obesity class changes. At the 12-Month follow-up, subjects in the TPS Group,

on average, lost 30.9% of their excess body weight compared to 9.8% in the Control Group, with an observed difference of 21.1% EWL between the two (2) groups. The mean weight loss was 21.1 lbs. (ranging from a weight loss of 81.2 lbs. to a weight gain of 8.1 lbs.) in the TPS group compared to 6.3 lbs. (ranging from a weight loss of 51.1 lbs. to a weight gain of 20.1 lbs.) in the Control group.

At the 12-month follow-up visit, 52.4% (88/168) of subjects in the TPS Group achieved at least one obesity class reduction compared to 28.1% (25/89) in the Control group, and 16.7% vs. 9.0% of subjects transitioned into non-obese BMI categories in the TPS and Control groups, respectively.

Table 14. Decrease in %EWL, Weight, BMI, and Obesity Class at 12 Months

		PP Population			mITT Population		
		TPS (N=168)	**Control (N=89)**	**Difference TPS-Control**	**TPS (N=171)**	**Control (N=89)**	**Difference TPS-Control**
%EWL	LS Means*(SE) 95% C.I.	30.9 (2.2) 26.6 to 35.3	9.8 (3.0) 3.9 to 15.6	21.2 (3.7) 13.9 to 28.4	30.2 (2.2) 25.8 to 34.6	10.3 (3.0) 4.4 to 16.2	19.9 (3.7) 12.5 to 27.2
Weight Loss(Ibs)	LS Mean(SE) 95% C.I.	21.1 (1.5) 18.3 to 24.0	6.3 (1.9) 2.4 to 10.1	14.8 (2.4) 10.1 to 19.6	20.5 (1.5) 17.6 to 23.6	6.3 (1.9) 2.4 to 10.1	13.9 (2.4) 9.0 to 18.7
BMI Reduction (kg/m^2)	LS Means(SE) 95% C.I.	3.5 (0.2) 3.0 to 3.9	1.0 (0.3) 0.4 to 1.6	2.5 (0.4) 1.7 to 3.2	3.4 (0.2) 2.9 to 3.9)	1.1 (0.3) 0.5 to 1.7	2.3 (0.4) 1.5 to 3.1
Obesity Class Reduction	N (%) 95% C.I.	88 (52.4%) 44.8% to 60.0%	25 (28.1%) 18.8% to 37.4%	24.3% 12.3%-36.3%	89 (52.1%) 44.6% to 59.5%	25 (28.1%) 18.8% to 37.4%	24.0% 12.0% to 35.9%

**Least Squares mean*

Changes in Cardiometabolic Risk Factors, Quality of Life, and Eating Inventory
The changes in cardiometabolic risk factors, quality of life, and eating inventory from baseline to 12 months were predetermined secondary endpoints; however, no confirmatory statistical hypothesis testing was pre-defined with these endpoints.

Changes in blood pressure parameters in patients with baseline elevated blood pressure by group are shown in **Table 15;** changes in the total cholesterol, LDL, and triglycerides in patients with a baseline hyperlipidemia (Total Cholesterol ≥ 200 mg/dL, LDL ≥ 130 mg/dL, Triglycerides ≥ 150 mg/d) by group are shown in **Table 16**.

Table 15. Changes in Blood Pressure at 12-Month in Subjects with Hypertension at Baseline (mITT Population)

		TPS	Control	Difference TPS-Control
DBP ≥ 80 mmHg at baseline	N	110	52	
	Baseline (Mean, SD)	86.9 (5.7)	87.6 (5.3)	
	12-Month LS Means Change (SE) 95% C.I.	-5.4 (0.82) -7.0 to -3.8	-0.9 (1.2) -3.3 to 1.4	-4.5 (1.4) -7.3 to -1.6
SBP ≥ 130 mmHg at baseline	N	90	46	
	Baseline (Mean, SD)	140.6 (7.8)	141.2 (8.0)	
	12-Month LS Mean Change (SE) 95% C.I.	-8.2 (1.3) -10.7 to -5.6	-0.4 (1.8) -4.0 to 3.2	-7.8 (2.2) -12.2 to -3.4

Table 16. Changes in Clinical Laboratory Values in Subjects with Elevated Baseline Values (mITT Population)

		TPS	Control	Difference TPS-Control
LDL ≥ 130 mg/dL at baseline	N	52	31	
	Baseline (Mean, SD)	152.7 (21.7)	154.3 (26.1)	
	12-Month LS* Mean Change (SE) 95% C.I.	-15.2 (3.7) -22.7 to -7.7	1.7 (4.9) -8.0 to 11.3	-16.7 (6.1) -29.1 to -4.7
Total Cholesterol ≥ 200 mg/dL at baseline	N	68	42	
	Baseline (Mean, SD)	227.5 (30.2)	231.0 (32.7)	
	12-Month LS Mean Change (SE) 95% C.I.	-13.6 (3.9) -21.3 to -5.8	-4.4 (4.9) -14.1 to 5.3	-9.2 (6.2) -21.6 to 3.2
Triglycerides ≥ 130 mg/dL	N	51	26	
	Baseline (Mean, SD)	213.4 (54.6)	230.2 (109.7)	
	12-Month LS Mean Change (SE) 95% C.I.	-47.2 (9.2) -65.5 to -28.8	-28.5 (13.2) -54.9 to -2.2	-18.6 (16.1) -50.9 to 13.6

**Least Squares mean*

Quality of Life

Obesity-related quality of life outcomes as measured by IWQOL-Lite were in favor of the TPS-treatment compared to Control in Total Score and Dimensions of Physical Function, Self-Esteem, Sexual Life, and Work. The Public Distress outcomes were similar in both groups.

Eating Inventory

Eating Inventory was used to assess subject's eating behavior. At 12-Month follow-up, the TPS group performed better in Cognitive Restraint and

Disinhibition than the Control group. Subjects in the TPS group also showed lower Hunger scores at 6 months.

3. Subgroup Analyses
   No pre-procedure characteristics were evaluated for potential association with outcomes.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR Part 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included nine (9) principal investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology-Urology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The ENDObesity II pivotal study had two (2) co-primary effectiveness endpoints, both of which were met. These endpoints demonstrated that the TransPyloric Shuttle/TransPyloric Shuttle Delivery Device was more effective than a medically supervised diet and exercise program alone for 12 months. At the 12-Month follow-up, the %TBL was 9.5% for the TPS group compared to 2.8% in the Control group ($p < 0.0001$). The difference in %TBL between TPS and Control groups was 6.7% (95% C.I., 4.5 to 8.8). At the 12-month follow-up, the proportion of TPS subjects who achieved ≥ 5%TBL was 66.8% (95% CI: 59.3% to 74.3%).

B. **Safety Conclusions**

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above.

There were no deaths and no subjects experienced any irreversible complications. There were nine (9) device- or procedure-related SAEs in six (6) treated subjects. Among them, seven SAEs in five (5) subjects were related to TPS in residence, which resolved following endoscopic TPS removal, and one esophageal rupture that occurred during an unsuccessful delivery attempt and was associated with the development of a pneumothorax. The device- or procedure-related SAE rate was 6/213 subjects in whom the TPS placement was attempted (2.82%, 95% C.I. 1.30%, 6.01%). The most frequent SAE was gastric impaction that occurred in 4/203 treated subjects (1.97%).

Almost all (99%) of TPS subjects had at least one device-related AE during the study. The most commonly reported device-related adverse events were gastrointestinal events, with the majority mild to moderate in severity. The incidence of procedure-related events was similar in both groups (63.9% vs. 62.9% in TPS and Control groups, respective); most commonly oropharyngeal pain associated with the procedure.

The most frequent AEs among TPS subjects were nausea (63.1%) with a median duration of 3 days, upper abdominal pain (62.6%) with a median duration of 5 days, vomiting (58.1%) with a median duration of 2 days and dyspepsia (54.7%) with a median duration of 13 days. Erosive gastritis occurred in 13.3% of TPS subjects of which there were no severe events. Gastric ulcers occurred in 10.3% of TPS subjects of which 3/23 events (13%) were reported as severe AEs.

Among the 270 ITT patients (181 TPS and 89 Control), 131 TPS and 79 Control patients completed the 12 month study. Among the 203 subjects who received the TPS device, 44 (21.6%) exited the study and had the device removed prior to the 12-month follow-up visit. Two (2) additional TPS subjects had the device retrieved within the 12-month visit window due to AEs, and they were considered in the context of early device retrieval. Of the 46 subjects, 22 of them had their device retrieved at or prior to 180 days, while 24 of them underwent device retrieval after 180 days, corresponding to a device removal rate of 10.8% (22/203) at 6 months and 22.7% (46/203) overall. Early exit due to AEs occurred in 30/203 (14.8%) TPS subjects and 1/89 (1.1%) Control subjects. An additional 16 TPS and nine (9) Control subjects exited prior to the 12-month visit for reasons other than AEs (moving away, unwilling to comply with study visits, pregnant, etc.) The AEs that led to early exit in TPS subjects (30 subjects) included device-related SAEs in five (5) subjects, an unrelated SAE in one subject, and non-serious AEs in 24 subjects.

C. **Benefit-Risk Determination**

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The %TBWL delta between treatment and control of 6.54% is comparable to other endoscopic/intragastric devices intended for weight loss. The Per-Protocol TPS treated subjects had a mean baseline weight of 224 lbs. and experienced a mean %TBWL of 6.7% more thant did Control subjects. This is an approximate weight loss over 12 months of 15 lbs on average more than Control subjects. The mITT population experienced a mean %TBWL of 6.5% more than did Control subjects. The percentage of TPS (PP) treated subjects who achieved ≥5% TBWL was 66.8%; whereas, the mITT cohort was 66.1%. Co-primary endponts of the clinical study were met.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The device- or procedure-related SAE rate was 6/213 subjects in whom the TPS placement was attempted (2.8%, 95% C.I. 1.30%, 6.01%). The most frequent SAE was gastric impaction that occurred in 4/203 treated subjects (1.97%). The most serious SAE was an esophageal rupture with an associated pneumothorax which was related to an improper operator use during the placement of the device. This has a low likelihood of occurrence with adequate operator training. The remaining SAEs were related to abdominal pain, nausea, and vomiting. With the exception of the esophageal rupture and resulting pneumothorax, the SAEs were all reversible by removing the device. The use of the TPS device has an acceptable safety profile in view of the patient benefits.

Additional factors that address uncertainty and other aspects of benefit and risk for the TransPyloric Shuttle/TransPyloric Shuttle Delivery Device included:

- Overall, 46/203 TPS subjects had the device removed early (22.7%). This high removal rate may impact patient's ability to fully benefit from use of the device. This also creates moderate uncertainty in the benefit and risk associated with device use.

- White females accounted for a high percentage of study subjects: 72.4% of the TPS group and 73.0% of the Control group. Generalizability of the results in the non-white and male populations is unknown.

- Per the study design, the effectiveness analysis population were those that completed the study (Per-protocol). However, the ITT population would have been more representative of real-world users. The analyses in the mITT and ITT populations support that the results may be indicative of what real-world users may expect. These analyses are acceptable to support the robustness of the benefit of the device.

The current non-surgical options available for weight loss in patients with obesity vary in effectiveness and mechanisms of action. This device provides an additional therapeutic option.

1. Patient Perspectives
   Patient perspectives considered during the review included:

   Obesity-related quality of life outcomes were measured by IWQOL-Lite. Results were in favor of the TPS-treatment compared to Control in Total Score and Dimensions of Physical Function, Self-Esteem, Sexual Life, and Work. The Public Distress outcomes were similar in both groups.

In conclusion, given the available information above, the data support that for weight reduction in adult patients with obesity with a BMI of 35.0-40.0 kg/m^2 or a BMI of 30.0 to 34.9 kg/m^2 with one or more obesity-related comorbid conditions in conjunction with a diet and behavior modification program, the probable benefits outweigh the probable risks.

D. **Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of the TransPyloric Shuttle/TransPyloric Shuttle Delivery Device when used in accordance with the indications for use. Subjects treated with the TPS lost on average 9.5% of their baseline weight compared to 2.8% weight loss in Control subjects. About 67% of subjects treated with the TPS lost at least 5% of their baseline weight. The safety profile for the TransPyloric Shuttle/TransPyloric Shuttle Delivery Device is reasonable, with six (6) subjects experiencing nine (9) device- or procedure-related SAEs among 213 subjects in whom TPS placement was attempted in the ENDObesity II pivotal study. Most AEs were mild or moderate and were reversible with device removal. In conclusion, the TransPyloric Shuttle/TransPyloric Shuttle Delivery Device is safe and effective in the treatment of obesity in patients with BMI between 35.0 and 40.0 kg/m^2 or a BMI of 30.0-34.9 kg/m^2 with on or more obesity-related comorbid conditions when used in conjunction with a diet and behavior modification program.

XIII. CDRH DECISION

CDRH issued an approval order on April 16, 2019. The final conditions of approval cited in the approval order are described below.

In addition to the Annual Report requirements, continued approval of the PMA is based, in part, on your completion of a post-approval study. You are required to do the following:

- enroll your first study subject no later than 6-months after device commercialization (commercialization being when the first device is shipped);
- enroll and treat at least 50 subjects within 12-months of commercialization;

- enroll and treat at least 130 subjects within 18-months of commercialization;
- complete enrollment and treatment of at least 260 subjects within 26-months post-commercialization;
- ensure at least 200 subjects reach 12-month completion in the treatment phase of the study by 39 months post-commercialization;
- ensure at least 100 subjects reach 18-month completion in the weight-loss maintenance phase of the study by 46 months post-commercialization;
- and submit a final report to the Agency within 53 months post-commercialization.

You must provide the following data in post-approval study (PAS) reports. A PAS Progress Report must be submitted for this study every six (6) months during the first two (2) years of the study and annually thereafter, unless otherwise specified by FDA. The report, identified as a "PMA Post-Approval Study Report" in accordance with how the study is identified below and bearing the applicable PMA reference number, must be submitted to the address below.

PMA Post-Approval Study - In accordance with 21 CFR 814.82, the ENDObesity PAS Study is a multicenter, open-label study for the continuing evaluation and periodic reporting of the safety and effectiveness of the TransPyloric Shuttle for weight reduction in obese adults 22 years and older with a BMI of 30-40 kg/m^2. Subjects will be treated with the TransPyloric Shuttle/TransPyloric Shuttle Delivery Device in conjunction with a behavioral modification program. During the treatment phase, subjects will be followed for 12 months or until device removal, whichever occurs earlier. During the weight-loss maintenance phase, all subjects who lost at least 5% Total Body Weight Loss (TBWL) prior to device removal will be followed for an additional 6 months.

Patients who meet the inclusion/exclusion criteria and sign the informed consent to participate in the study will be enrolled. A minimum of 260 patients will be enrolled at up to 15 U.S. sites. Evaluation of at least 200 subjects is required at 12 months post-treatment. A sample size of 260 implanted subjects will provide 99% power to test the hypothesis that the rate of device- and/or procedure-related serious adverse events (SAEs) is less than 6% at 12 months with a test margin of 4%. The minimum acceptable number of evaluable subjects through the weight-loss maintenance phase is 100.

A secondary study objective is to demonstrate that the mean percent Total Body Weight Loss (%TBWL) is greater than 7% at 12 months.

Other study endpoints include the following: proportion of subjects who achieve at least 5% and 10% TBWL, weight loss measured by percent excess weight loss (%EWL), change of BMI from baseline, proportion of subjects who achieve at least one obesity class reduction, change in obesity-related comorbid conditions, device- and/or procedure-related adverse events, incidence of gastric ulcers, early device explants, and weight-loss maintenance at 3- and 6-months post device removal.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.