Endoscopic Treatment for Weight Reduction in Patients with Obesity Using the TransPyloric Shuttle® System: A Multicenter, Prospective, Randomized, Double-Blind, Sham-Controlled, Parallel-Design Study (ENDObesity® II Study)

Protocol number DTC006

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Contents

1. PROTOCOL SUMMARY

Protocol Title	**ENDObesity II Study**: Endoscopic Treatment for Weight Reduction in Patients with Obesity Using the TransPyloric Shuttle® System: A Multicenter, Prospective, Randomized, Double-blind, Sham-controlled, Parallel-design Study
Protocol Number	DTC006
Investigational Device	TransPyloric Shuttle® System (TPSS)
Proposed Indication	The TransPyloric Shuttle System is indicated for weight reduction in 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.
Regulatory Status	The device is under clinical investigation in the US for the proposed indication stated above.
Objectives	The objective of this study is to assess the safety and effectiveness of the TransPyloric Shuttle (TPS®) for weight reduction in obese subjects with BMIs of 30-40 kg/m^2.
Study Design	This is a multicenter, prospective, randomized, double-blind, sham-controlled, parallel-design study conducted in the United States. The pivotal study cohort will consist of 270 pre-planned study subjects which will be randomized in 2:1 ratio to the Treatment or the Control group from up to 12 sites. Subjects who sign the informed consent and are deemed eligible following a general and endoscopic screening will be enrolled in the study and randomized. Subjects assigned to the Treatment group will receive the TPS placement and the subjects in the Control group will undergo a sham procedure without TPS placement. The subjects will be blinded to their treatment. The Investigators and/or study coordinators who collect the primary outcome data will be masked to subjects' treatments. Subjects will be followed for 12 months or less than 12 months if the subject achieves the midpoint of the normal BMI range (22 kg/m^2), at which time the subject is considered to have completed the study and the device removed if the subject had received the TPS device. Subjects will receive brief (15 minute) lifestyle-modification counseling sessions at each follow up visit. They also will receive brief (15min) telephone calls in the months that do not include in person visits between 6 and 12 months (in months 7, 8, 10, and 11). These counseling sessions are centrally designed to improve adherence to recommendations to consume a healthy diet and increase physical activity to promote weight loss and overall health. The counseling sessions and telephone calls will be provided by a member of the research team (dietitian, nurse, etc.) trained in the delivery of the prescribed lifestyle counseling.
Patient Population	Male and female subjects, 22-60 years of age, with a BMI of 35.0 to 40.0 kg/m^2, inclusive, or a BMI of 30.0 to 34.9 kg/m^2 with at least one obesity-related comorbidity.

Co-Primary Endpoints	• Mean percent total body weight loss (% TBL) 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% TBL at 12 months after the index procedure.
Secondary Endpoints	• Proportion of subjects who achieve at least 7% and 10% TBL at 12 months in the Treatment versus Control group • Percent total body weight loss over 12 months in the Treatment versus Control group • Percent excess weight loss over 12 months in the Treatment versus Control group • Proportion of subjects who achieve at least one obesity class reduction at 12 months in the Treatment versus Control group • Change of BMI over 12 months from baseline in the Treatment group • Change in weight-related quality of life over 12 months as assessed by IWQOL-Lite Questionnaire • Change in eating behavior over 12 months as assessed by the Eating Inventory • Change in appetite, hunger and fullness over 12 months as assessed by Visual Analog Scales • Change in comorbid conditions over 12 months in the Treatment group: o Prevalence of the metabolic syndrome and its individual components o Glucose, insulin, and insulin resistance (as estimated by HOMA) o High sensitivity C-reactive protein (hsCRP) o Lipid levels (LDL-C, HDL-C, and triglycerides) o Blood pressure o Waist circumference
Safety Evaluation	Safety will be characterized through a summary of the incidence of adverse events. A Clinical Event Committee (CEC) will review and adjudicate all serious device-related adverse events and any other events deemed necessary.
Key Inclusion Criteria	1. Male and female subjects between the ages of 22 to 60 2. A BMI between 30.0 to 40.0 kg/m^{2,} inclusive. Subjects with a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 are required to have one or more of the following obesity-related mild-moderate comorbidities: a. Type 2 Diabetes: meet one of the following criteria and currently not using insulin i. HbA1c 6.5%-7.5% ii. Controlled, on stable dose of oral medications for at least 3 months b. Hypertension, meet one of the following criteria: i. Arterial blood pressure >140 mmHg systolic or >90 mmHg diastolic on or off hypertensive medication ii. Arterial blood pressure ≤140 mmHg systolic and ≤90 mmHg diastolic on hypertensive medication c. Hyperlipidemia, meeting at least one of the following criteria: i. Fasting blood total cholesterol level of ≥240 mg/dl ii. Fasting total triglyceride level of ≥200 mg/dl

	iii. Low density Lipoprotein cholesterol ≥160mg/dl iv. Currently taking lipid-lowering medication based on an elevation of total cholesterol, triglycerides, or LDL 3. History of obesity for at least 2 years, with history of failure of medically or commercially supervised weight loss program 4. History of weight stability (defined as a < 5% change in body weight) for at least 3 months prior to the screening visit 5. Female subjects of childbearing potential must have a negative urine pregnancy test and must commit to practice their physician-agreed form of birth control for the duration of participation 6. Willing and able to provide written informed consent 7. Willing and able to comply with study procedures and return for all study visits
Key Exclusion Criteria	1. Pregnancy or planned pregnancy in next 12 months after enrollment 2. Nursing or pregnancy within the 6 months prior to enrollment 3. Known hormonal or genetic cause for obesity 4. Prior history of any surgery or endoscopic intervention that has altered esophageal, gastric or duodenal anatomy, including any bariatric surgery, such as gastric bypass, and restrictive procedures such as laparoscopic adjustable gastric banding 5. Prior treatment with an intragastric balloon for the purpose of weight loss, where the balloon was removed less than 12 month prior to the screening visit for this study 6. Chronic use (at least past 6 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) 7. A history of gastric or duodenal ulcers 8. After treatment for *Heliobacter pylori*, subject still tests positive for *H. pylori* 9. A history of severe dyspepsia 10. GI tract motility disorders such as esophageal motility disorders, gastroparesis diabeticorum, or intractable constipation 11. History of inflammatory disease of GI tract, such as Crohn's disease 12. History of coeliac disease 13. History of pancreatitis 14. History of portal hypertension, cirrhosis, and/or varices 15. Diabetes treated with insulin or significant likelihood of requiring insulin in next 12 months 16. HbA1c >7.5% 17. Uncontrolled thyroid and adrenal gland disease 18. Uncontrolled hypertension defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg 19. A history of cardiac arrhythmia, ischemic heart disease, myocardial infarction or chronic heart failure 20. History of cerebrovascular disease, transient ischemic attack, or stroke 21. Presence of localized or systemic infection 22. Anemia (hemoglobin <11.0 g/dl for female and <12.0 g/dl for male)

	23. History of asthma likely to require systemic steroid therapy during the duration of the study participation or frequent use of rescue inhalers 24. Autoimmune connective tissue disorders or known to be immunocompromised or at risk of becoming immunocompromised (e.g., HIV positive) 25. A history of malignancy except non-melanoma skin cancer 26. Continuous therapy with known ulcerogenic medication (e.g., aspirin greater than 81mg/day, NSAIDs) 27. On anticoagulation or antiplatelet therapy (e.g., Coumadin, Warfarin, Heparin, Pradaxa, Xarelto, Plavix) 28. Unwilling to avoid use of any weight-loss medication, including over-the-counter treatments and/or herbal supplements, during the course of 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) 29. Currently participating, or unwilling to avoid participation in any non-study-related organized weight-loss program (medical or commercial) during the course of the study 30. Unable to take proton pump inhibitor (a daily 40+mg of Omeprazole or equivalent), or addition of PPI may cause adverse drug interaction with subject's medication or interruption of treatment 31. Clinically significant abnormal laboratory values or an EKG that make the subject a poor study candidate in the opinion of the Investigator 32. Inability to walk at least 0.8 kilometers per day (10 minutes of continuous walking) 33. Planned surgical procedure that can impact the conduct of the study 34. Started on a prescribed medication regimen within the last three 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 35. Known allergy to any component materials in the TPSS such as silicone, barium sulfate, parylene 36. Current smoker or user of nicotine product or smoking cessation within 1 year of the screening date 37. Current abuse of drug or alcohol or past treatment for substance abuse 38. Presence of any severe, uncontrolled psychiatric illness 39. Inpatient psychiatric treatment within the past year 40. A score of ≥10 on the Patient Health Questionnaire 9 (PHQ-9), indicating moderate depression 41. Diagnosis of bulimia nervosa or binge eating disorder 42. Any medical condition (including psychiatric disease) 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. 43. Participation in another clinical study within 60 days of screening date, in previous or ongoing clinical study, or plan to participate in another clinical study at any time during this study

	44. Employee or family member of BARONova, the Investigator, or site study staff 45. The Investigator judges the candidate unsuitable for the study 46. Have any of the following endoscopic exclusion criteria a. Esophageal stricture b. Barrett's esophagus c. Erosive esophagitis d. Varices e. Angiectasias f. Gastric mass g. Antral or peri-pyloric polyps h. Peptic ulceration i. Hiatal hernia ≥ 4 cm j. Pyloric stricture k. Any other abnormalities/characteristics that would preclude safe use of the TPS
Post Procedure Follow-up and Assessment Schedule	• Office visits: 1 week, and 1, 2, 4, 6, 9, and 12 month(s) • Endoscopic follow up [redacted] • Blood tests: 6 and 12 months • Eating Inventory and Visual Analog Scales: 1 week, and 1, 6, 12 months • IWQOL-Lite: 6 and 12 months • Device removal: 12 months
Analysis Population	Intent-to-Treat: includes all randomized and enrolled subjects regardless of whether or not the subject receives the randomized treatment. Per -Protocol: includes all subjects who receive the assigned treatment and do not have any major eligibility violations. Modified Intent-to-Treat: consists of the Intent-to-Treat population that have received the assigned treatment and have at least one post-treatment follow up, including the index procedure visit. Completed Cases: includes all enrolled subjects who have the 12-month follow-up visit, or have completed the study based on reaching the BMI objective of ≤ 22 kg / m^2 in two consecutive follow-up visits as described in Section 5.1.
Proton Pump Inhibitor (PPI) Use	Subject will be placed on PPI (Omeprazole 40 mg daily or equivalent) starting at least one week before the index procedure and continue until the TPS removal (or the last visit in the Control subjects).
Post Procedure Patient Management	• Subject will be on a liquid diet for 3 days, followed by soft food for 7 days, and then a normal diet. • Subject will have antiemetic and antispasmodic on standby.
Safety Monitoring	Safety will be monitored throughout the study. The Investigators will assess the occurrence of adverse events at each follow up visit. The Data Safety Monitoring Board (DSMB) will monitor and evaluate the safety data throughout the study. A pre-specified staged safety monitoring will be performed after the first 30, 60 and 90 subjects in the Treatment group have reached 80 days post index procedure.
Timeline	• First Subject Enrolled: Q4 2015 • Estimated Enrollment Duration: 12 months (Q4 2016) • Last Subject to Primary Endpoint Follow-up: (Q4 2017)

	• Study Duration: 24 months

2. BACKGROUND

Obesity is a major public health issue in the United States with 78 million adults now obese. In 2009-2010, the prevalence of obesity in the US was 35.5% among men and 35.8% among women.[1] The annual healthcare costs associated with obesity have been estimated at up to 8% of overall healthcare budgets. Recognizing the health consequence and the morbidity and mortality associated with obesity, the American Medical Association officially classified obesity as a disease in 2013.[2]

2.1. Definition of Obesity

Obesity is defined as a body mass index (BMI) that exceeds 30 kg/m^2. A BMI of 18.5-25 kg/m^2 is defined as normal and 25-30 kg/m^2 as overweight. Obesity is further classified into three groups: moderate (Class I, BMI 30.0 – 34.9), severe (Class II, BMI 35.0 – 39.9), and very severe (Class III, BMI > 40).[3]

2.2. Obesity Related Comorbidities and the Benefit of Modest Weight Loss

Substantial evidence suggests that obesity is associated with significant morbidity and mortality. A comprehensive systematic review and meta-analysis including 87 high quality prospective cohort studies concluded that excess body weight was associated with the incidence of multiple comorbidities, including Type 2 diabetes mellitus, cardiovascular diseases, cancers, asthma, osteoarthritis and gallbladder disease.[4] A BMI ≥30 kg/m^2 is also associated with reduced life expectancy.[5,6]

Weight loss has been shown to improve many of the comorbidities associated with obesity and results in significant improvements in components of the metabolic syndrome.[7,8,9] A weight loss as small as 3% can result in improvements in some cardiovascular disease risk factors and a weight loss of 5% or more is generally considered to be clinically meaningful.[10,11] A loss of 5% to 10% of body weight is associated with decreased cardiovascular disease risk factors, prevention or delay of the development of Type 2 diabetes, and improvement of other health consequences of obesity.[12,13] Greater weight loss produces greater reductions in cardio metabolic risk.[14] The recently published 2013 AHA/AAC/TOS Guideline recommends a chronic disease management model for obesity, in which patients are encouraged to lose 5% to 10% of their body weight as an initial goal to decrease the risk of the development, or amelioration of, obesity-related medical conditions and cardiovascular risk factors.[15]

2.3. Treatment Options

2.3.1. Lifestyle Modification Interventions

Lifestyle modification focuses on caloric reduction, increased physical activity, and behavioral modification strategies. Lifestyle intervention by itself results in moderate weight loss. Although studies performed in academic centers have shown that intensive lifestyle modification delivered in weekly counseling sessions can produce a 7-10% weight loss and improvements in weight-related health problems within 6 months, the "real world" outcomes are often more modest and are largely influenced by the delivery methods, intensity, and duration of the interventions. A recent example of this is the POWER-UP study which randomized 390 subjects into three types of intervention: usual care, consisting of quarterly primary care provider (PCP) visits that included education about weight management; brief lifestyle counseling, consisting of quarterly PCP visits combined with brief monthly sessions with lifestyle coaches who instructed participants about behavioral weight control; or enhanced brief lifestyle counseling, which also provided quarterly physician visits and monthly lifestyle counseling sessions but included the use of meal replacement products or weight-loss medication. The change in body weight (% TBL) with usual care, brief lifestyle counseling, and enhanced

brief lifestyle counseling was 2.1% ± 0.6%, 3.5% ± 0.6%, and 7.0% ± 0.6% at 1 year (P<0.001), and 1.6% ± 0.6%, 2.9% ± 0.7%, and 4.7% ± 0.6% (P<0.001) at 2 years, respectively.[16]

Outcomes of lifestyle modification interventions are greatly influenced by patient motivation as well as adherence and compliance over time. It is, however, important to recognize that lifestyle modification is an essential component of any weight loss intervention, including pharmacotherapy and bariatric surgery.

2.3.2. Pharmacotherapy

Pharmacotherapy for weight loss is often used as a more intensive treatment for obesity after lifestyle modification fails. Pharmacotherapy is typically recommended for patients with a BMI > 30 kg/m^2 or > 27 kg/m^2 in the presence of weight related comorbidities and when weight-loss goals and related health improvements were not achieved with lifestyle modification.

When combined with lifestyle interventions, obesity medications can produce a moderate weight loss ranging from approximately 3% of initial weight for orlistat and lorcaserin to 9% for top-dose (15/92 mg) phentermine plus topiramate–extended release at 1 year. Mean total weight loss ranges from 1% to 5% of placebo-subtracted values, and varies based on factors including patient population and intensity of concomitant lifestyle intervention.[17] Thirty percent to more than 60% of patients may not achieve a clinically meaningful weight reduction (5%) at 12 weeks. [17]

Adverse effects of weight loss medications range from headache, nausea, fatigue, and dizziness to more severe concerns such as cardiovascular events and birth defects. During the history of antiobesity drugs, many have been withdrawn in the United States secondary to concerns with their side effects. Various guidelines recommend prescribing drug therapy for obesity after thorough consideration of potential risks against potential benefit for each individual patient. The cost effectiveness of long-term pharmacotherapy of obesity is still an unresolved question.

2.3.3. Bariatric Surgery

Patients with BMIs ≥ 40 kg/m^2 or ≥ 35 – 39.9 kg/m^2 with significant weight-related co-morbidities, and who have failed more conservative weight-loss treatments (such as lifestyle modification and pharmacotherapy), are potential candidates for bariatric surgery[15]. The most common surgical procedures include gastric bypass surgery, sleeve gastrectomy, and adjustable gastric banding procedures. Patients lose 50%-60% excess body weight (EWL) with the gastric bypass procedure and 40%-50% with restrictive procedures at 2 years. The Swedish Obesity Subjects (SOS) study[13,18] is a landmark investigation that provided high quality evidence on the long-term effect of bariatric surgery. It included 4,047 obese subjects, prospectively matched between three surgical interventions (1471) and the control group (1444). The surgically treated subjects underwent nonadjustable or adjustable banding (n = 376), vertical banded gastroplasty (VBG; n = 1369), or gastric bypass (GBP; n = 265). All three types of surgeries produced larger weight losses than seen in the control group. In addition, the study demonstrated patterns of initial maximum weight loss at 1-2 years and subsequent weight regain over time (**Figure 1**). A more recent longitudinal study from the US (LABS-2) showed similar results to those observed in the Swedish study over 3 years of follow up, with 31.5% total weight loss for Roux-en-Y gastric bypass (RYGB) and 15.9% for laparoscopic adjustable gastric band (LAGB)[19].

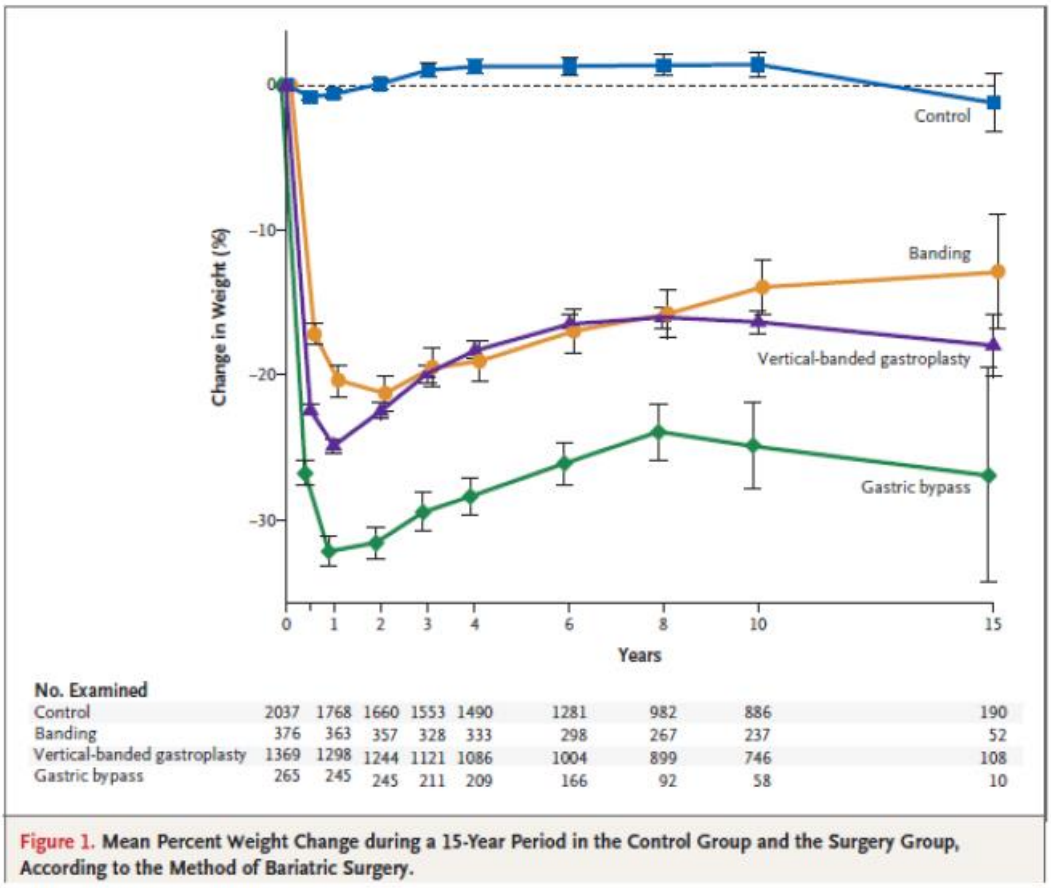


Figure 1. Mean Percent Weight Change during a 15-Year Period in the Control Group and the Surgery Group, According to the Method of Bariatric Surgery.

Figure 1. Long-term Weight Loss after Bariatric Surgery in SOS Study

While surgery is most effective in weight loss, a significant proportion of patients experience surgical complications. Early post-operative complications include leak, bleeding, stricture, perioperative blood loss and reoperation occurring in 5-10% of patients. Colquitt et al.[20] conducted a detailed analysis of complications in a systematic review of surgical studies. Operative re-intervention occurred in 13% of surgical patients, laparoscopic revision (10%), port infection (2.6%) and acute cholecystitis (2.6%). The SOS study[13] reported complications of operative death (0.25%), perioperative complications (13%), infection (2.1%), pulmonary symptoms (6.2%), thromboembolism (0.8%) and bleeding (0.9%). Late complications including anemia and B12 deficiency, have been reported in at least 25% of patients.[21] Vomiting and gastric dumping have been reported in one- to two-thirds of patients. The mortality rate is generally thought to be approximately 1%.

Despite the success often seen with bariatric surgery, only 1% of the clinically eligible population receives surgical treatment for obesity.[22,23] This is likely due to many factors, including lack of insurance coverage for the procedures, as well as perceived risks of the procedures among potential patients and their providers. Regardless of the specific reasons, there is a need for additional, effective treatments to promote weight loss in patients with obesity.

2.3.4. Endoscopic Approaches to Obesity

Endoluminal interventions performed entirely through the GI tract by using flexible endoscopy offer the potential for an ambulatory weight-loss procedure that may be safer and more cost-effective when compared to current surgical approaches. A number of innovative devices are currently in development and are at various stages. The only device that was previously approved in the US was the Garren-Edwards Gastric Bubble®, which was sold in the U.S. market from 1985 to 1987. The device was subsequently removed from the US market by the manufacturer because of a high rate of device deflation and subsequent GI obstructions. The BioEnterics Intragastric Balloon (BIB or Orbera®) and similar intragastric balloon devices are currently available outside the US.

Intragastric balloons are designed to be an adjunctive therapy to lifestyle modification. The device typically remains within the stomach for up to 6 months. Patients undergo intensive lifestyle modification during the treatment period and afterwards, with the hope that the device will provide the patient with a window of opportunity to develop eating and activity habits that can be used to maintain weight loss once the device is removed.

A meta-analysis[24] pooled 15 articles (3,608 patients) and showed that the intragastric balloon intervention achieved 12.2% of total weight loss and 32.1% of excess weight loss at balloon removal. A recently published randomized study[25], which compared intragastric balloon plus lifestyle intervention to lifestyle intervention alone, rendered similar results with 14.2% TBL in the intragastric balloon group versus 4.8% in the lifestyle modification alone at 6 months. Genco et al[26] reported a multicenter experience of 261 patients treated with the intragastric balloon that were followed up to 3 years. The mean BMI fell from 28.6 $kg/m^2 \pm 0.4$ kg/m^2 at baseline to 25.4 $kg/m^2 \pm 2.6$ kg/m^2 at 6 months and to 27.0 $kg/m^2 \pm 3.1$ kg/m^2 at 3 years from BIB removal. The mean %EWL was 55.6% at 6 months and 29.1% at 3 years. Despite a weight regain after balloon removal, improvements in comorbidities were observed at 3 years, with hypertension decreasing from 29% at baseline to 16% at 3 years, diabetes from 15% to 10%, dyslipidaemia from 20% to 18%, hypercholesterolaemia from 32% to 21% and osteoarthropathy from 25% to 13%.

Common adverse effects include intractable nausea and vomiting affecting over 70% of patients, resulting in patient intolerance and early device removal in 4.2% of patients[26]. Other complications include balloon leaking/deflation, obstruction, gastritis, and gastric or duodenal ulcerations.

2.3.5. Weight-Loss Maintenance

Weight regain following a successful weight-loss intervention historically has been a challenge for all types of weight loss treatments. A typical pattern of weight loss in patients undergoing a lifestyle intervention is that maximum weight loss is achieved at 6 months, followed by a plateau and gradual regain over time. A similar pattern is observed in medication-assisted weight loss when medication is stopped. For bariatric surgery patients, maximum weight loss occurs within 1 year followed by gradual weight regain overtime, as shown in Figure 1. For example, gastric bypass patients had a maximum weight loss of 38% TBL at one year, followed by a weight regain of about 13% with maintenance of a 25% body weight loss at 10 years.

Recently published AHA/ACC/TOS Guideline[15] advises individuals who have lost weight to participate in a long-term (≥1 year) comprehensive weight-loss maintenance program to enforce lifestyle modification in order to maintain weight loss.

It is increasingly recognized that treating obesity requires a range of effective therapies, and combinations of these therapies are often required to provide long-term control. While bariatric surgery is the most effective weight-loss therapy, it carries significant short-term and long-term morbidities and costs. Pharmacotherapy in combination with lifestyle intervention can only achieve modest weight reduction while carrying the potential of systemic side effects of pharmacologic agents. In order to effectively manage the epidemic of obesity and reduce the societal burden of the associated co-morbidities, there is an urgent need for therapies that are safer, less invasive, and reversible while providing clinically meaningful weight loss to patients. In this study, we aim to evaluate an endoscopic, non-surgical interventions using the BAROnova TransPyloric Shuttle System.

3. DEVICE DESCRIPTION

The investigational device is the TransPyloric Shuttle System (TPSS). The TPSS has undergone three generations of device iterations. The current study device represents the third generation device (GEN III TPSS).

3.1. System Description

The TransPyloric Shuttle System consists of a TransPyloric Shuttle (TPS), its delivery system, and the TPS Retrieval Kit. The TPS is designed to be delivered into and removed from the gastric cavity using a trans-esophageal endoscopic procedure.

3.1.1. TransPyloric Shuttle

The TPS is constructed of three main components: the external skin, the inner coil and the lock-release button. These components are preloaded into the TPS Delivery Device. During the TPS delivery, the three components are mechanically joined to construct the functional configuration of the TPS device. [redacted]

After being 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 (Figure 2). [redacted]

The TPS is principally made of a medical-grade silicone elastomer and the internal coil is loaded with barium sulfate for radiopacity. The external surface is coated with parylene.

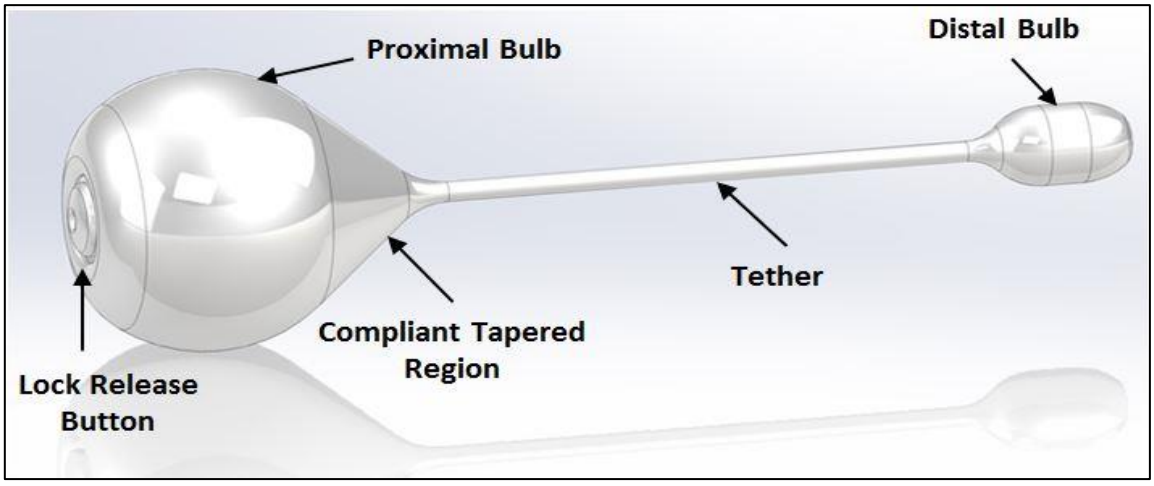


Figure 2. TransPyloric Shuttle

Figure 3. [redacted]

3.1.2. TPSS Delivery System

The TPS Delivery System consists of the TPS Delivery Device (Figure 4) and the TPSS Access Sheath (Figure 5). Both are designed for single-use and are disposed after the procedure.

BARONova also provides a reusable TPSS Accessory Kit for use with the Delivery System that includes: an insufflation system, a TPSS stand, [redacted] and a hook tool. The insufflation system is designed to provide pressure-controlled air to the stomach to insufflate the gastric space during deployment. The TPSS stand and tools facilitate use and troubleshooting of the system.

3.1.2.1. TPSS Delivery Device

The TPS Delivery Device is designed for trans-esophageal delivery of TPS through the TPSS Access Sheath. The Delivery Device consists of [redacted], a proximal handle that controls the delivery mechanism, [redacted], and an access-sheath connector that enables secure engagement with the proximal end of the Access Sheath for device positioning (Figure 4). 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. [redacted]

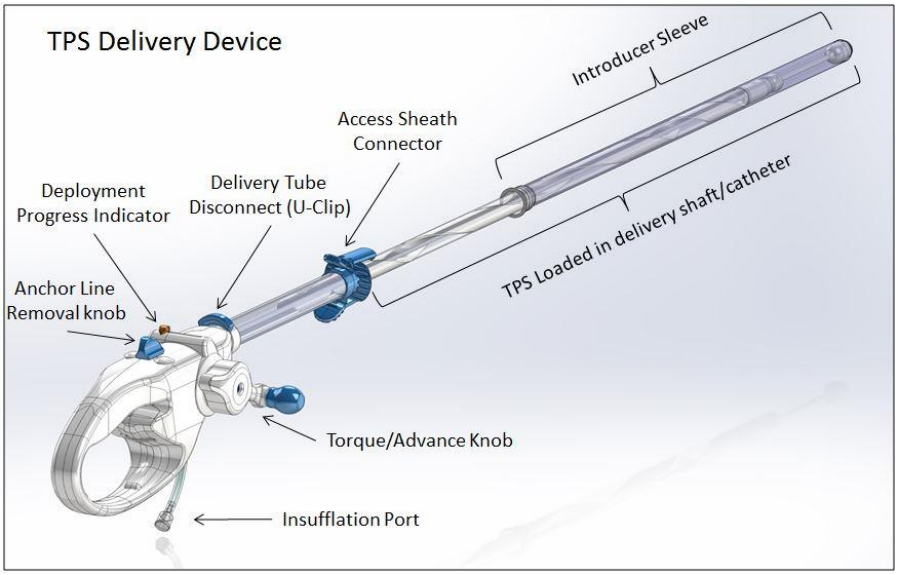


Figure 4. TPSS Delivery Device

3.1.2.2. TPSS Access Sheath

The TPSS Access Sheath consists of a [redacted] with a [redacted] distal positioning balloon and an obturator. It is designed to protect the esophagus during the TPS delivery procedure. After inflation, the distal balloon is positioned against the gastroesophageal junction under endoscopic visualization. This sets the position for TPS deployment. Once the Delivery Device is fully inserted, its Connector engages the Access Sheath handle, and the system is ready for deployment.

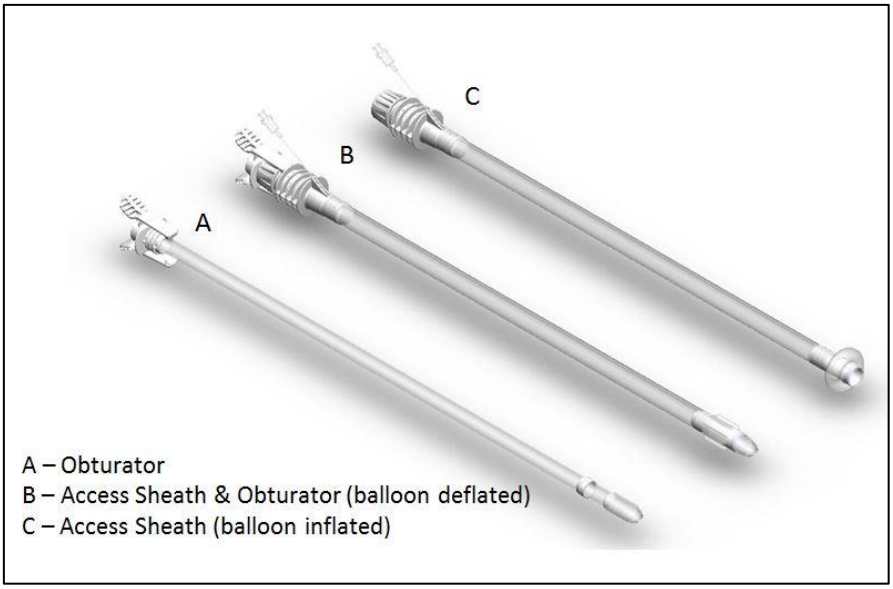


Figure 5. TPSS Access Sheath

3.1.2.3. TPSS Accessory Kit

The TPSS is provided with a reusable TPSS Accessory Kit to facilitate deployment of the device. The primary components of the Accessory Kit are described below.

Figure 6. TPSS Stand with TPS Delivery Device in Place

For the convenience of the operator, the handle of the TPS Delivery Device may be placed in the reusable, stand (Figure 6) for deployment. Once the Access Sheath has been placed and the TPS Delivery Device is fully-inserted into it with the connectors engaged, the system is ready for deployment.

Prior to initiating TPS coil advancement with the handle controls, the TPS Delivery Device is connected to the reusable insufflation system using the disposable tubing set provided with the system. [redacted]

Figure 7. [redacted]

3.1.3. TPS Retrieval Kit

[redacted]

BARONova will provide a TPS Retrieval Kit [redacted] intended to facilitate endoscopic removal of the TPS device. [redacted]

Figure 8 [redacted]

The TPS Retrieval Kit is composed of single-use items that are disposed after the retrieval procedure.

Figure 8. [redacted]

Figure 9 illustrates the overtube when assembled for insertion with the retrieval accessories as well as close up views of the tip configured for insertion (gastroscope is not shown) and the tip insert component.

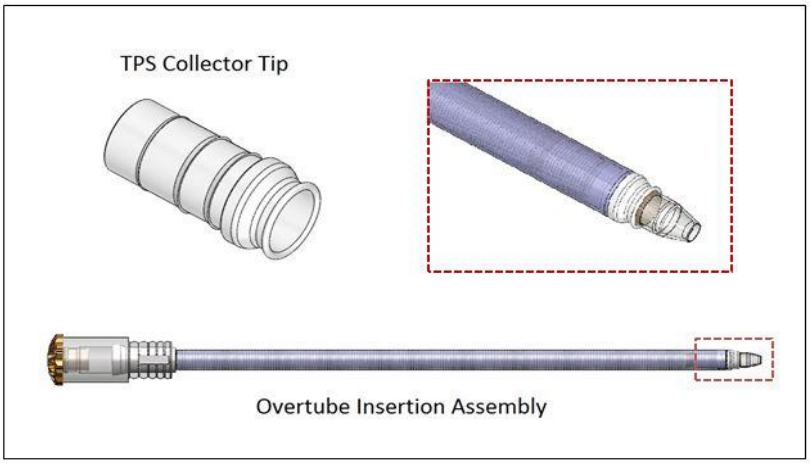


Figure 9. Overtube Insertion Assembly

3.2. Proposed Mechanism of Action

The TPS is delivered directly into the gastric cavity in a non-surgical, endoscopic, outpatient procedure. Once delivered, the device is designed to self-position across the pylorus and create an intermittent obstruction to outflow that may result in delayed gastric emptying (Figure 10). Slowing gastric emptying may enable an overall reduction in caloric intake and weight loss by helping the subject feel full sooner (early satiation) and/or feel full longer (prolonged satiety/reduced hunger). While in residence in the stomach, the TPS may also affect mechanisms near the gastric outlet and in the proximal duodenum to augment feelings of fullness.

The device is mainly constructed in medical-grade silicone with a small volume and light weight, thus minimizing intolerance symptoms as seen in intragastric balloon devices.

The TPS is designed to be a removable device. The device residence time is 12 months in the current study. After which time, the TPS is removed in a non-surgical, endoscopic, outpatient procedure. The strategies for weight maintenance after device removal should follow clinical practice guidelines for weight loss maintenance.[15]

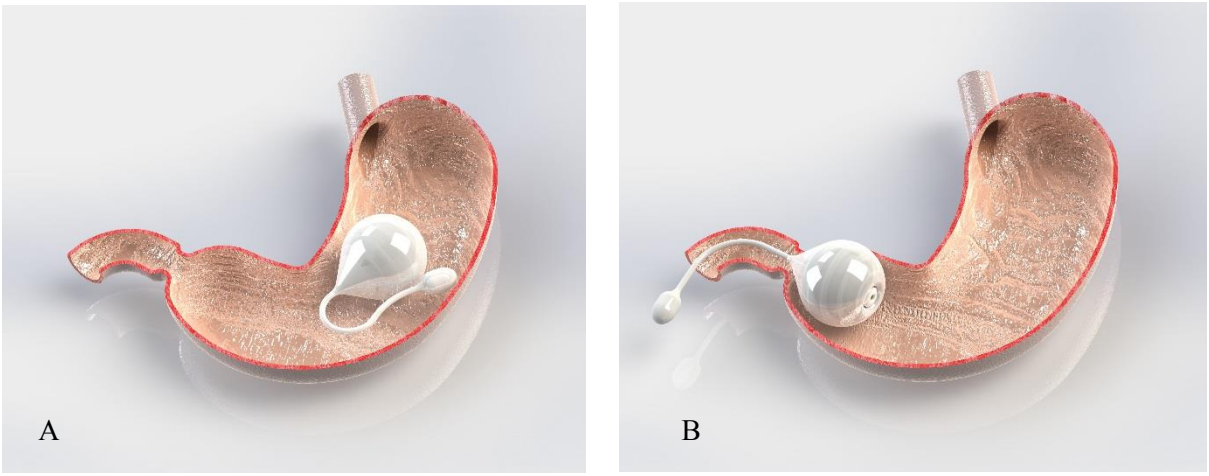


Figure 10. TPS in Gastric (A) and Transpyloric (B) Position

3.3. Proposed Indication

The TransPyloric Shuttle System is indicated for weight reduction for 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.

3.4. Prior Investigations

3.4.1. Pre-Clinical Testing

Development of the TPSS includes a preclinical testing program intended to ensure safe use of the system in human studies for weight loss. TPS device testing is based on the anticipated biomechanical environment associated with one-year residence. Delivery system and device-retrieval testing is based on the anatomical and operational requirements in an outpatient setting employing endoscopically-based, non-surgical, transesophageal procedures.

The BARONova quality system requires that the TPSS final product configuration meets all specifications in the TPSS Product Specification prior to human use. The testing also demonstrates that all risks identified in in the TPSS Risk Analysis, which is developed in accordance with ISO 14971:2007, have been adequately mitigated. Preclinical bench testing verifies system performance relative to a broad spectrum of system characteristics, including but not limited to:

- Biocompatibility
- Durability, including acute strength, cyclic fatigue, and material composition
- Simulated use
- Shelf life/package integrity

Acute animal studies in porcine and canine models are performed to validate comprehensive simulated use bench testing for system functionality in delivery and retrieval. Chronic studies performed in live pigs demonstrated successful endoscopic deployment and retrieval of the TPS and robustness of the device in the gastric environment.

A similar pre-clinical testing program was utilized to characterize the previous iteration of the TPSS that was used in the ENDObesity I clinical study. In the ENDObesity I study, devices were safely delivered and successfully retrieved from 10 subjects after three months of residence time, and from 10 subjects after six months. Retrieved devices were returned to BARONova and evaluations of device integrity were performed. These evaluations showed:

- No gross damage or component failures after device residence
- No changes in mass or gross dimensions
- No significant changes to the mechanical properties of the materials of construction of the device

The performance of the TPSS in the ENDObesity I study provides validation of BARONova's pre-clinical testing program to produce a safe and robust system for use in human clinical trials.

3.4.2. Biocompatibility Testing

The TransPyloric Shuttle System is comprised of the TransPyloric Shuttle device, the TPS delivery system and a TPS Retrieval Kit.

The TPS device is evaluated in accordance with the requirements of ISO 10993-1: 2009, Biological Evaluation of Medical Devices to ensure that the devices are suitable for the anticipated exposure to human mucosal tissues.

The required biocompatibility evaluation for the system is performed on device samples that are manufactured with the materials and processes representative of the device that will be used in the proposed IDE pivotal clinical trial. All tests performed are managed in accordance with the FDA Good Laboratory Practices (GLP) regulation (21 CFR Part 58).

The TPS device is evaluated as a "surface device" with "mucosal membrane contact" of greater than 30 days duration. As the TPS may also come into contact with irritated mucosa in the stomach, testing for a "surface device" for "breached or compromised surface" of contact duration of greater than 30 days is also considered.

The TPSS Delivery System is composed of the TPS delivery device and Access Sheath and is evaluated as a "surface device" with "mucosal membrane contact" with contact duration of less than 24 hours.

The TPS Retrieval Kit is designed to be used with the commercially available gastric overtube for TPS retrieval. Components in the TPS Removal Accessory Kit are also evaluated as a "surface device" with "mucosal membrane contact" with contact duration of less than 24 hours.

An evaluation of the TPSS has been performed which included a review of existing data on the same materials previously tested and used in the GEN II TPSS in addition to confirmatory testing on any new materials in the current device. All of the materials in the GEN III TransPyloric Shuttle System have been tested and assessed per the requirements of ISO 10993-1:2009. The acceptable data confirmed that the GEN III TransPyloric Shuttle System meets the biocompatibility requirements per ISO 10993:2009 and is safe and suitable for human use as intended.

3.4.3. Prior Clinical Experience

A feasibility study (ENDObesity I Study) was conducted in 20 subjects in a single-center study that evaluated the safety and effectiveness of the second generation TPSS. The study included male and female obese subjects, 18 to 55 years of age, with a BMI 35-50 kg/m^2 or 30-34.9 kg/m^2 with one or more obesity-related

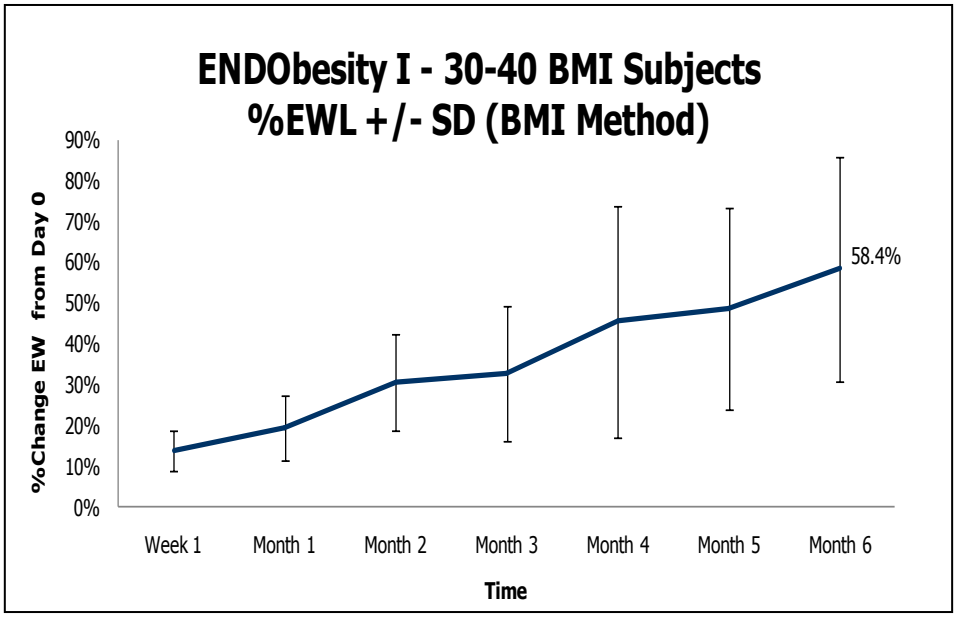
comorbid conditions. The key exclusion criteria included pregnancy, previous gastrointestinal bariatric surgery, GI motility disorder, severe psychiatric conditions, and clinically important comorbid diseases such as insulin-dependent diabetes and uncontrolled hypertension. Subjects with significant endoscopic abnormalities (such as gastroduodenal ulcer, hiatal hernia ≥ 2cm, and erosive esophagitis) were also excluded. Subjects were assigned to two groups of ten subjects. The device residence time was 3 months in first group of 10 subjects and 6 months in the second group of 10 subjects. The primary effectiveness endpoint was percent excess weight loss (EWL). The Impact of Weight on Quality of Life-Lite Questionnaire (IWQOL-Lite) was used to assess patient weight-related quality of life status before and after the treatment.

Subjects were provided nutritional guidelines and encouraged to increase their physical activity at the beginning of the study. No specific dietary or exercise counseling was provided during the study duration after the initial baseline consultation.

The average age of the subjects was 40.7 years ± 10.7 years and 18/20 (90%) were female. The baseline weight was 100.9 kg ± 20.5 kg, with a mean BMI of 36 kg/m^2 ± 5.5 kg/m^2 (34.0 kg/m^2 ± 4.9 kg/m^2 and 37.9 kg/m^2 ± 7.3 kg/m^2 for 3- and 6-month subjects, respectively). Baseline comorbidities included gastroesophageal reflux (50%), osteoarthritis (45%), hypertension (20%), Type 2 diabetes (5%), and sleep apnea (5%).

TPS devices were successfully deployed and removed endoscopically in all subjects with no device or procedure related SAEs peri-procedurally. Mean procedure times were 10.9 minutes ± 3.9 minutes for device deployment (from TPSS insertion to system removal) and 12.9 minutes ± 6.4 minutes for device removal (from overtube insertion to TPS and overtube removal).

The excess weight loss was 33.1% ± 18.7% for the 3-month subjects and 50.0% ± 26.4% for the 6-months subjects. Those who had the device for 3 months lost, on average, 8.9 kg of weight (8.9% of TBL). Those who had the device for 6 months lost, on average, 14.6 kg (14.5% of TBL). All 10 subjects (100%) who had the device for 6 months achieved at least 5% TBL and 80% of them achieved more than 10% TBL. The weight-loss curve in the target patient population (BMI 30-40 kg/m2) is shown in Figure 7.



(N=17 for week 1 through month 3; N=7 for months 4-6)

Figure 11. %EWL in Proposed Target Population of 30-40 BMI Subjects

Statistically significant improvements in the IWQOL-Lite overall scores were observed for both the three-month and six-month cohorts. Mean increases of 23.5 and 23.6 points in the 3-month and 6-month study groups greatly exceeded the 7.7 to 12 point threshold considered to define a clinically significant change[27].

The device was well tolerated by patients. There were no deaths, no major gastrointestinal events such as bleeding or perforation, and no surgical interventions for any complications. Device-related adverse events were mostly mild to moderate in nature, including transient abdominal pain (8/20), nausea (6/20), vomiting (4/20), GERD (4/20), feeling heaviness (2/20), sore throat (1/20), constipation (1/20), candidiasis (1/20), pyloric spasm (1/20) and bloating (1/20). [redacted]

3.5. Risks and Benefits

3.5.1. Potential Benefits

There are clear potential benefits for subjects who participate in this clinical study. Subjects to be included in the present study have an existing indication for weight loss. The majority of these subjects may have attempted weight loss by diet or other means at some point in their life. The potential benefit of participating in this study is the ability to achieve clinically-significant weight loss without the need for bariatric surgery.

There are potential societal benefits to a successful study. Obesity and its associated comorbidities is a widely recognized global problem that consumes a large amount of health care resources. If the device is shown to be safe and effective, it will provide a therapy that fills the gap between lifestyle intervention and bariatric surgery in terms of their risk and effectiveness profile, and thus contribute to overall management of obesity.

3.5.2. Anticipated Adverse Events (AEs) Associated with the TPS Placement, Residence, and Removal

Anticipated AEs associated with the TPS placement and removal procedures and TPS residence may include, but are not limited to, the following:

- Abdominal cramps and discomfort from the air used to distend the stomach
- Aspiration of gastric contents, aspiration pneumonia
- Complications related to sedation and anesthesia
- Complications related to upper GI endoscopy and the use of routine endoscopic instruments
- Infection in the throat, esophagus, stomach, or duodenum
- Gastric, esophageal, or pharyngeal trauma, including sore or irritated throat, ulceration, bleeding, or perforation in upper GI tract, and their associated complications

- Injury to the digestive tract by the TPS delivery system or during device removal
- TPS placement in an improper location such as in the esophagus or duodenum, which results in obstruction, bleeding, or perforation
- Esophageal sphincter and/or pyloric sphincter incompetency associated with sphincter dilation during placement, residence or removal of the TPS
- Inability to endoscopically remove part or all of the TPS device, which may result in the need for surgery
- Cardiac or respiratory arrest during endoscopy
- Halitosis
- A feeling of heaviness in the abdomen
- Abdominal or back pain, either steady or cyclic
- Gastric discomfort, feelings of nausea, and vomiting
- Constipation or diarrhea
- Dyspepsia
- Allergic reaction to the device's materials (e.g., silicone, barium sulfate and parylene)
- Excess reduction in oral intake, resulting in dehydration or malnutrition
- 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.
- Influence on digestion of food
- Pharyngeal, esophageal, or gastrointestinal obstruction by the TPS
- Formation of intragastric bezoars
- Gastroesophageal reflux
- Distension of stomach
- Injury or irritation to upper GI tract, resulting in acute or chronic tissue inflammatory response, pain, bleeding, erosion, ulceration, strictures, stenosis, or perforation
- Bacterial or fungal growth on the surfaces of the TPS, resulting in infection
- Biliopancreatic infection or obstruction, cholecystitis, pancreatitis
- Need for medication, endoscopic intervention, early TPS removal, or surgery to treat/correct complications
- Death

3.5.3. Residual Risks Associated with the Investigational Device, as Identified in the Risk Analysis Report

BAROnova has conducted extensive assessment of the risk associated with the device. The conclusion of the current risk assessment is that, with respect to perceivable conditions in which the product would be subjected to a worst-case environment or human error scenario, the outcome of the residual risk is considered acceptable as none of the recognized hazards leads to a risk within the intolerable range.

The risk assessment does not contain foreseeable risks of intolerable levels. The device is designed and manufactured such that, when used as intended, it will not compromise the conditions of safety of the patients or operator, and any remaining risk is managed with a high level of protection of subject safety.

3.5.4. Risks Associated with Participation in the Clinical Investigation

There are risks associated with participation in a clinical investigation. There is only limited clinical experience with the device to date and there may be unanticipated adverse events. There are protocol-defined tests and follow-up studies such as endoscopy that may carry additional risk to the subjects. In addition, this is a sham-controlled, double-blinded study. The sham procedure and the blinding may carry additional risk to the subjects.

3.5.5. Possible Interactions with Concomitant Medication

The effect of the TPS device to the absorption of orally administered medication is unknown. The physician should evaluate the risk and benefit of this procedure for patients who take concomitant medications and carefully monitor the patients.

Patients who receive hypoglycemic or anti-hypertension agents should be monitored closely as their medication dosages may need to be adjusted with the decrease in food intake and weight loss.

3.5.6. Minimization of Risks

The following steps have been taken to further minimize the risks of the study:

- The study protocol has built in measures to control potential adverse effects, including study inclusion/exclusion criteria, prophylactic medications, clinical and endoscopic surveillance, guidelines for post-procedure management, and provisions for early removal of the device if necessary.
- Patient informed consent contains sufficient information on the potential risks.
- Subjects will be provided with subject information cards that contain brief device and physician contact information if needed
- Unblinding is permitted when the Investigational Device information is necessary for the management of adverse events and ensuring subject's safety
- Training and technical support will be provided for device placement/removal procedures in the study
- A DSMB is set up to monitor the safety of the study

In summary, subjects included in the present study have a clinical indication for weight loss. Prior clinical experience shows that the device can be deployed successfully, that subjects achieve significant weight loss over a 3-6 month residence time, and that the complications can be managed clinically. The risks associated with the device have been mitigated to the extent possible. The current study design includes additional measures to further minimize risks. These data and study design features indicate a favorable risk-benefit profile for the subjects to be included in the present study.

4. STUDY OBJECTIVES

The objective of this study is to demonstrate the safety and effectiveness of the BARONova TransPyloric Shuttle for weight reduction in patients with BMIs of 30-40 kg/m^2 compared with the sham-control over the 12 months treatment period.

The study will also assess, as secondary endpoints, changes in weight-related comorbidities, weight-related quality of life, and eating behavior.

The study will be considered a success for efficacy purposes if it meets both of the primary efficacy analyses.

The safety will be characterized, with all adverse events reported. The Clinical Event Committee (CEC) will adjudicate all serious device-related adverse events and any other events deemed necessary.

5. STUDY DESIGN

5.1. Study Design

This is a multicenter, prospective, randomized, parallel design, double-blinded, sham-controlled study. A total of 270 subjects are planned for the pivotal study cohort. Subjects meeting the general inclusion/exclusion criteria will undergo baseline endoscopic assessment. Those who meet endoscopic eligibility will be randomized in a 2:1 allocation to the Treatment or Control group stratified according to center. The Treatment group will receive the TPS placement and the Control group will receive a sham endoscopic procedure that does not include TPS placement.

Subjects will be followed up for 12 months after the index procedure or until the device is removed.

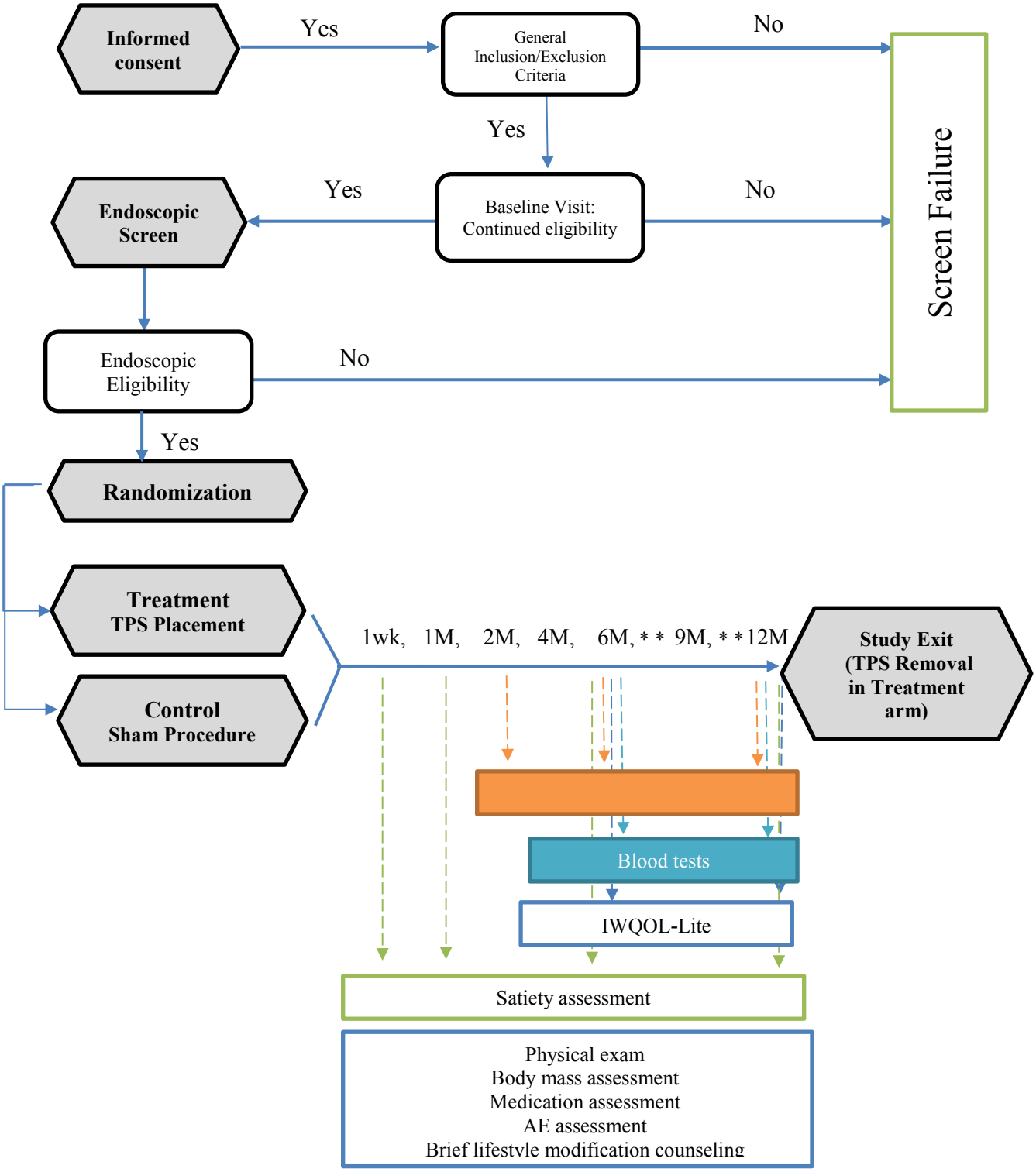
At 12 months, subjects in the Treatment group will undergo an endoscopic assessment followed by the TPS removal. Subjects in the Control group will complete all the same assessments as the Treatment group except the endoscopy.

Subjects who achieve a BMI of ≤ 22 kg/m^2 for two consecutive visits before the 12-months follow up will be considered a treatment success, have the device removed if in the Treatment group, and exit the study. A BMI of 22 kg/m^2 is selected as a reference value since it is a midpoint value of the normal BMI range, and a BMI ≥ 23 kg/m^2 has been shown to be associated with an increased risk of developing diabetes in the Nurses' Health Study that followed 43,581 women over 8 years.[28] The handling of these subjects in the analysis is described in Section 15.5.

Subjects in both groups will receive the same lifestyle modification education and counseling during the 12-month follow up duration. In brief, subjects will receive written instruction in lifestyle modification strategies for weight loss (e.g., caloric restriction, increasing physical activity, behavioral modification, etc.) at the beginning of the study. At each follow up visit, subjects will receive a brief (15 minute) lifestyle modification counseling performed by a medical provider (i.e., registered dietitian, nurse, behavioral health specialist)

trained in the delivery of the intervention. In months 7, 8, 10, and 11 where an in-person follow-up visit is not scheduled, site provider will have a brief (15 minute) telephone call with the subject. During these calls, the provider and patient will discuss changes in weight, diet, eating behavior and physical activity over the past month. These calls are designed to promote adherence to the lifestyle modification strategies previously taught to the subject.

A schematic diagram of the study design is shown in Figure 12.



*telephone contacts at 7, 8, 10, 11M

Figure 12. Study Diagram

5.2. Subject Recruitment and Enrollment

Subjects will be recruited by Investigators at each study site. Candidates may be recruited during routine office visits; by IRB-approved advertisements such as brochures, flyers, letters, and other methods in the individual sites; or by referral from IRB-approved sponsor's advertisements in newspapers, radio, the internet, or other methods. Candidates who are potentially eligible for the study will be scheduled for a screening visit.

After giving written informed consent, subjects will undergo screening assessments. As part of the recruitment and enrollment process, potential participants will undergo a behavioral/psychosocial evaluation similar to that performed prior to bariatric surgery, as recommended by the American Society for Metabolic and Bariatric Surgery, and required by most third party payers for reimbursement for bariatric surgery. [29] This clinical assessment will include direct questioning about the potential participants psychosocial status (with specific focus on symptoms of disordered eating and depression), mental health treatment history, and a review of the potential participant's current diet and regular eating behaviors. This evaluation is designed to assess for the presence of significant psychopathology that would contraindicate weight loss treatment and/or successful participation in the study. The evaluation will be performed by a member of the study team (registered dietitian, behavioral specialist, mental health professional, etc.) who will be trained by a consultant to the study with extensive expertise in the psychosocial and behavioral aspects of obesity and bariatric surgery. This consultant also will provide periodic supervision to the individuals performing these evaluations and to ensure that the sites are using similar criteria to evaluate and include/exclude study participants.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the general exclusion criteria will be scheduled for a baseline visit within one week of the planned procedure. Subjects who remain eligible after the baseline visit will be scheduled for the procedure.

On the day of the procedure, subjects will undergo endoscopic assessment to confirm endoscopic eligibility. Subjects who meet the endoscopic exclusion criteria will be excluded from the study and will be considered a screening failure. Subjects who meet the endoscopic eligibility will be randomized using a web-based randomization tool provided by the study data management organization. A TPSS Access Sheath is placed allowing delivery of the TPS during the same procedure. TPS is delivered in the treatment group but not in the control group.

A subject is considered enrolled in the study when the subject has given written informed consent and the TPSS Access Sheath has been placed in the subject.

5.3. Randomization and Masking

Eligible subjects will be randomized to either the Treatment or the Control group in a 2:1 ratio stratified according to center. Randomization will be according to a random permuted block design within strata. Block size of 3 and 6 will be used.

Randomization occurs on the day of the procedure after endoscopic screening. The Investigator who performs the index procedure and endoscopic follow-ups will not collect the primary outcome data. The Investigator and/or the study coordinator who collect the primary outcome data will be masked to the subject's intervention.

The subject will be blinded to the intervention for the duration of participation in the study.

The Clinical Event Committee (CEC) will be masked to the subject's intervention. The Data Safety Monitoring Board (DSMB) will have access to unmasked subject data, as required, to monitor and evaluate the safety data throughout the study.

5.4. [redacted]

[redacted]

5.5. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.6. Early Study Termination

Sponsor may discontinue the study at any stage for any reason or no reason. Possible reasons for early termination may include unanticipated adverse device effects that may present unreasonable patient risk.

The Study Steering Committee assists Sponsor in making a final decision for early study termination based on Data Safety Monitoring Board (DSMB) recommendations (refer to Section 14).

If the study is terminated early, the sponsor will provide a written statement describing why premature termination has occurred, and notify the Investigator, Institutional Review Board (IRB) and the regulatory authority (if applicable). All applicable clinical study documents will be subject to the same retention policy as detailed in Section 17.

5.7. Measures Taken to Avoid/Minimize Bias

This is a randomized, double-blinded, and sham-controlled study. The study design minimizes the bias of placebo effect, patient selection, and the effect of lifestyle intervention. The outcome data will be collected by the Investigator or study coordinator who are masked to the intervention, thus minimizing Investigator bias.

Subjects in both groups and at all study sites will be provided with the same lifestyle educational materials. Site personnel will be trained in the delivery of the centrally prescribed lifestyle modification intervention prior to the onset of the study and will receive ongoing supervision during the study to ensure treatment fidelity across study sites.

An independent Clinical Events Committee (CEC) will be established to adjudicate safety events as described in Section 13. The CEC will be masked to the subject's intervention, thus minimizing bias in safety assessment. A Data Safety Monitoring Board (DSMB) (Section 14) will be established to monitor and evaluate the safety data throughout the study.

6. STUDY ENDPOINTS

6.1. Primary Effectiveness Endpoints

The effectiveness of the TPS will be assessed by the following co-primary endpoints:

- Mean percent total body weight loss (% TBL) 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% TBL at 12 months after the index procedure.

6.2. Secondary Effectiveness Endpoints

The following secondary endpoints will be assessed in this study:

- Proportion of subjects who achieve at least 7% and 10% TBL at 12 months in the Treatment versus Control group
- Percent total body weight loss over 12 months in the Treatment versus Control group
- Percent excess weight loss over 12 months in the Treatment versus Control group
- Proportion of subjects who achieve at least one obesity class reduction at 12 months in the Treatment versus Control group
- Change of BMI over 12 months from baseline in the Treatment group
- Change in weight-related quality of life over 12 months as assessed by IWQOL-Lite Questionnaire
- Change in eating behavior over 12 months as assessed by the Eating Inventory
- Change in appetite, hunger and fullness over 12 months as assessed by Visual Analog Scales.
- Change in comorbid conditions over 12 months in the Treatment group:
  a) Prevalence of the metabolic syndrome and its individual components
  b) Glucose, insulin, and insulin resistance (as estimated by HOMA)
  c) High sensitivity C-reactive protein (hsCRP)
  d) Lipid levels (LDL-C, HDL-C, and triglycerides)
  e) Blood pressure
  f) Waist circumference

6.3. Safety Evaluations

The overall device safety profile is characterized by assessing the incidence of adverse events (AEs), serious adverse events (SAEs), serious adverse device effects (SADEs), and unanticipated serious adverse device effects (UADEs) as detailed in Section 12. No formal hypothesis testing will be performed.

7. PATIENT SELECTION AND WITHDRAWAL

7.1. Study Population

Subjects with a BMI of 30.0-40.0 kg/m^2 who meet the inclusion and exclusion criteria will be evaluated for participation in the study. To ensure the safety of the subjects during weight loss, we aim to enroll individuals with controlled weight-related co-morbidities, such as Type 2 diabetes, hypertension, and hyperlipidemia. Conversely, individuals with a recent cardiovascular event and those with serious internal organ disease will be excluded.

The pivotal study cohort will consist of 270 subjects that will be enrolled from up to twelve study sites in the US, with no one site enrolling more than 25% of the total number of subjects in the pivotal cohort.

7.2. Inclusion Criteria

1. Male and female subjects between the ages of 22 to 60
2. A BMI between 30.0 to 40.0 kg/m^2, inclusive. Subjects with a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 are required to have one or more of the following obesity-related mild-moderate comorbidities:
    a. Type 2 Diabetes: meet one of the following criteria and currently not using insulin
        i. HbA1c 6.5%-7.5%
        ii. Controlled, on stable dose of oral medications for at least 3 months
    b. 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 on hypertensive medication
    c. Hyperlipidemia, meeting at least one of the following criteria:
        i. Fasting blood total cholesterol level of ≥240 mg/dl
        ii. Fasting total triglyceride level of ≥200 mg/dl
        iii. Low density Lipoprotein cholesterol ≥160mg/dl
        iv. Currently taking lipid-lowering medication based on an elevation of total cholesterol, triglycerides, or LDL
3. History of obesity for at least 2 years, with history of failure of medically or commercially supervised weight loss program
4. History of weight stability (defined as a < 5% change in body weight) for at least 3 months prior to the screening visit
5. Female subjects of childbearing potential must have a negative urine pregnancy test and must commit to practice their physician-agreed form of birth control for the duration of participation
6. Willing and able to provide written informed consent
7. Willing and able to comply with study procedures and return for all study visits

7.3. Exclusion Criteria

1. Pregnancy or planned pregnancy in next 12 months after enrollment
2. Nursing or pregnancy within the 6 months prior to enrollment
3. Known hormonal or genetic cause for obesity
4. Prior history of any surgery or endoscopic intervention that has altered the esophageal, gastric, or duodenal anatomy, including any bariatric surgery, such as gastric bypass, and restrictive procedures such as laparoscopic adjustable gastric banding
5. Prior treatment with an intragastric balloon for the purpose of weight loss, where the balloon was removed less than 12 month prior to the screening visit for this study
6. Chronic use (in the past 6 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)
7. A history of gastric or duodenal ulcers
8. After treatment for *Heliobacter pylori*, subject still tests positive for *H. pylori*
9. A history of severe dyspepsia
10. GI tract motility disorders such as esophageal motility disorders, gastroparesis diabeticorum, or intractable constipation
11. History of inflammatory disease in the GI tract, such as Crohn's disease
12. History of coeliac disease
13. History of pancreatitis
14. History of portal hypertension, cirrhosis, and/or varices

15. Diabetes treated with insulin or significant likelihood of requiring insulin treatment in the next 12 months
16. HbA1c >7.5%
17. Uncontrolled thyroid and adrenal gland disease
18. Uncontrolled hypertension defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg
19. A history of cardiac arrhythmia, ischemic heart disease, myocardial infarction or chronic heart failure
20. History of cerebrovascular disease, transient ischemic attack or stroke
21. Presence of localized or systemic infection
22. Anemia (hemoglobin < 11.0 g/dl for female and < 12.0 g/dl for male)
23. History of asthma likely to require systemic steroid therapy during the duration of the study participation or frequent use of rescue inhalers
24. Autoimmune connective tissue disorders or known to be immunocompromised or at risk of becoming immunocompromised (e.g., HIV positive)
25. A history of malignancy except non-melanoma skin cancer
26. Continuous therapy with known ulcerogenic medication (e.g., aspirin greater than 81mg/day, NSAIDs)
27. On anticoagulant therapy (e.g., Coumadin, Warfarin, Heparin Pradaxa, Xarelto, Plavix)
28. Unwilling to avoid use of any weight-loss medication, including over-the-counter treatments and/or herbal supplements during the course of 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)
29. Currently participating or unwilling to avoid participation in any non-study-related organized weight-loss program (medical or commercial) during the course of the study
30. Unable to take proton pump inhibitors (a daily 40+ mg of Omeprazole or equivalent), or addition of PPI may cause adverse drug interaction with subject's medication or interruption of treatment
31. Clinically significant abnormal laboratory values or an EKG that make the subject a poor study candidate in the opinion of the Investigator
32. Inability to walk at least 0.8 kilometers per day (10 minutes of continuous walking)
33. Planned surgical procedure that can impact the conduct of the study
34. Started on a prescribed concomitant medication regimen within the last three 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
35. Known allergy to any component materials in the TPSS including silicone, barium sulfate, and parylene
36. Current smoker or user of nicotine product or smoking cessation within 1 year of the screening date
37. Current abuse of drug or alcohol or past treatment for substance abuse
38. Presence of any severe uncontrolled psychiatric illness
39. Inpatient psychiatric treatment within the past year
40. A score of ≥10 on the Patient Health Questionnaire 9 (PHQ-9), indicating moderate depression
41. Diagnosis of bulimia nervosa or binge eating disorder
42. Any medical condition (including psychiatric disease) 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
43. Participation in another clinical study within 60 days of screening date, in a previous or ongoing clinical study, or plan to participate in another clinical study at any time during this study
44. Employee or family member of BARONova, the Investigator, or site study staff
45. The Investigator judges the candidate unsuitable for the study

46. Have any of the following endoscopic exclusion criteria:
    a. Esophageal stricture
    b. Barrett's esophagus
    c. Erosive esophagitis
    d. Varices
    e. Angiectasias
    f. Gastric mass
    g. Antral or peri-pyloric polyps
    h. Peptic ulceration
    i. Hiatal hernia ≥ 4 cm
    j. Pyloric stricture
    k. Any other abnormalities or characteristics that preclude safe use of the TPS

7.4. Point of Enrollment

The point of enrollment occurs when a subject or subject's legally authorized representative has provided written informed consent and the TPSS Access Sheath has been introduced in the subject during the index procedure.

7.5. Patient Discontinuation

Once enrolled, each subject will remain in the study until the required follow-up period is complete. However, the subject has the right to withdraw from the study at any time without penalty or loss of benefit. The following events will result in terminating the subject's follow-up:

- Subject voluntary withdrawal
- Subject withdrawn by the Investigator as clinically indicated
- Subject becomes pregnant
- Subject lost to follow-up
- Subject death
- Study is terminated according to Section 5.6 (Early Study Termination)

In the case of subject withdrawal from the study, the TPS must be removed before the subject exits the study.

In case the TPS is removed early as described in Section 10.5, the subject's participation in the study is considered terminated. Any Adverse Events will be followed until resolution or stabilization according to Section 12.1.

In case a subject achieves normal BMI (≤ 22 kg/m^2) for two consecutive visits before the 12-month follow up, the subject is considered to have completed the study. Subject will exit the study and the device should be removed in the treatment subjects.

A final endoscopy should be performed whenever possible before the Treatment subject exits the study.

The Sponsor must be notified of the reason for subject discontinuation. The site will document this information on the electronic case report form (eCRF) and make every effort to give a full description of the reason for withdrawal. Investigators must also report this information to the local IRB as defined by their institution's procedure.

Subjects who are terminated early will not be replaced by enrolling additional subjects.

7.6. Lost to Follow-up

Subjects that do not complete the scheduled follow-up visits and have not officially withdrawn from the study are considered lost to follow-up; this term does not apply to missed visits. Site personnel should make

considerable effort to locate and communicate with the subject using all available methods (e.g., telephone, emails, and postal mail). The following contact procedure is recommended at each time point:

- A minimum of two telephone calls on different days over the specified follow-up windows should be recorded in the source documentation including date, time, and site personnel initials for the staff attempting to contact the subject.
- If these attempts are unsuccessful, a certified letter should be sent to the subject.
- If the subject misses two consecutive scheduled contact time points and the above mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost to follow-up.

While a subject becoming lost-to-follow-up must be considered a possibility, it is imperative that all subjects have the device removed, as the long-term response of the device materials to the stomach environment is not yet known.

8. LIFESTYLE INTERVENTIONS

The goal of the lifestyle modification counseling is to promote use and adherence to a reduced calorie diet (approximately 1500 kcal/d), increase physical activity (primarily through daily walking), and to recommend behavioral modification strategies.

This intervention is adapted from the Brief Lifestyle Counseling condition in the POWER-UP study[16] described previously. A detailed protocol for the lifestyle intervention is attached in Appendix C. Prior to the start of the study, study personnel from the study sites will participate in a training session which will focus on the delivery of the intervention. These study personnel also will participate in ongoing conference calls where they will receive supervision on the delivery of the lifestyle modification intervention to study participants.

8.1. Diet Recommendations

The diet recommendation will follow the recommendations of the Diabetes Prevention Program and as used in the POWER-UP study. Subjects who weigh ≤ 114 kg (≤ 250 lb) will be prescribed 1200-1500 kcal/d and those > 114 kg (> 250 lb) 1500-1800 kcal/d. All subjects will receive the same written information regarding food intake at lifestyle counseling sessions.

8.2. Physical Activity Recommendations

Subjects will be encouraged to increase their physical activity, performing such tasks as taking 10,000 steps a day, avoiding elevators and escalators, etc. No specific methods will be provided to enforce or facilitate subject compliance.

8.3. Behavior Modification

At the same time as the diet prescription and activity advice, subjects will be instructed in behavioral modification strategies to promote weight control and that can be used in their daily lives. Examples of these strategies include reducing food intake by using smaller plates, reducing consumption of high calorie beverages, putting the fork down between bites, etc. These are detailed in the Appendix C.

8.4. Telephone Contacts

In months 7, 8, 10, and 11, when subjects are not scheduled for an in-person follow up visit, subjects will participate in a brief (15-minute) telephone call with study site personnel providing the lifestyle modification counseling. During these calls, subjects will report on changes in weight, dietary intake, eating behavior, and physical activity level. These telephone calls are designed to promote adherence to the lifestyle modification protocol in the absence of in-person visits. The provider will reinforce positive behaviors consistent with the

lifestyle modification program and problem solve issues related to weight gain, increased caloric intake or decreases in physical activity.

9. CONCOMITANT MEDICATIONS

Concomitant medications deemed medically necessary for the subject will be allowed during the course of the study; however, any changes in medications will be documented on the Concomitant Medication Log. Medications used during the placement/removal of the TPS, such as anesthesia, will not be tracked via the Concomitant Medication Log.

9.1. Prohibited Concomitant Medications

9.1.1. Weight-Loss Medications

Study subjects will not be allowed to take any weight-loss products during the course of the study, including prescription, over-the-counter (OTC), and herbal products.

9.1.2. NSAIDs (Non-Steroidal Anti-inflammatory Drugs)

Subjects must be off NSAIDs and aspirin for at least two weeks prior to TPS placement and remain off for the duration of the study. Treatment with Acetaminophen may be continued. Low dose aspirin (81 mg/day) may be used if needed in combination with prophylactic PPI.

9.1.3. Other Medications

Medications affecting subject motility, such as Reglan and Erythromycin should be discouraged, but allowed if necessary.

9.2. Required Concomitant Medications

9.2.1. Proton Pump Inhibitors (PPIs)

Subject will be placed on Omeprazole at 40 mg once daily, or its equivalent starting at least one week before the index procedure and continue for 12 months until the TPS removal (or the last visit in the Control subjects). The dose may be adjusted based on the judgment of the Investigator. Use of the PPIs will be recorded on the Concomitant Medication Log.

10. POST PROCEDURE PATIENT MANAGEMENT

10.1. Managing GI Symptoms

Following the index procedure, the subject should be on liquid diet for three days, followed by soft food for a week, and then slowly return to a normal diet in ten days.

Clinical experience suggest the TPS therapy is well-tolerated by subjects. However, some subjects may experience nausea, vomiting, and bloating after the procedure. Antiemetic (such as Ondansetron) and antispasmodics (such as Butylscopolamine) should be provided on standby, and the subjects should be educated on their use.

In case of prolonged vomiting (more than 4-6 times in 24 hours), subjects should be evaluated and, if necessary, be managed with PO, IV fluid, and intravenous antiemetic.

In case of recurrent vomiting (every day over 3-5 days), abdominal pain, and non-response to medical management, the patient should be evaluated (including endoscopy if necessary) to rule out obstruction or an ulcer.

10.2. Managing Endoscopic Observations

Tissue effects such as erythema, erosions, or ulcers may be observed during endoscopic surveillance. Limited clinical experience to date suggests that some patients may be asymptomatic while others may develop symptoms.

10.2.1. Ulcer Definition

For the purpose of this study, an ulcer is defined as ≥ 5mm in diameter with unequivocal depth by endoscopy. Ulcer is defined as endoscopically significant if it is ≥ 3cm in length and ≥ 1cm in width. Ulcers will be classified as symptomatic or asymptomatic, complicated or uncomplicated. An ulcer is complicated if the patient develops clinical complications including bleeding, perforation or obstruction.

Efforts should be made to capture clear images with an accessory of known dimensions next to the lesion to estimate size.

10.2.2. Guidelines for Managing Endoscopic Observations

The following algorithm (

Figure 13) is suggested for managing endoscopic observations in subjects after the index procedure.

Figure 13. [redacted]

10.3. Managing Hypoglycemia Risks in Diabetic Subjects

Subjects with diabetes are potentially at risk of developing hypoglycemia during a weight loss study. The risk may be greatest upon initiation of dietary and device intervention. Among patients with diabetes who qualify for inclusion in this study, the risk of hypoglycemia is very low to absent in those managed with diet alone, and the risk is greater in patients treated with sulfonylureas, repaglinide or nateglinide, than in patients treated with other oral anti-diabetes agents. The following guideline is provided for minimizing severe hypoglycemia in diabetic subjects during the study. The treating physicians should exercise their clinical judgment for the treatment of individual subjects.

10.3.1. Subject Education

At the onset of the study, subjects with T2DM, regardless of diabetic medication regimen, should be educated on the potential for development of hypoglycemia, the symptoms and signs of hypoglycemia, instruction in the use of home blood glucose monitoring to detect hypoglycemia, and instruction on treating hypoglycemia. Symptoms suggestive of hypoglycemia include lightheadedness, tremor, shaking, sweating, tingling, blurred vision, difficulty concentrating, and confusion. With marked hypoglycemia, patients may develop altered consciousness, coma, or seizures. Subjects treated with anti-diabetic medication should self-monitor blood glucose (BG) in the first week post intervention and are encouraged to self-monitor BG throughout the study. Additionally, for subjects treated with sulfonylureas, repaglinide or nateglinide, self-monitoring of BG should be performed twice daily starting one week before the index procedure and continuing for a minimum of 4 weeks post-procedure or until stabilization of glycemic control. Subjects should be instructed to promptly contact site staff for any documented or suspected hypoglycemia.

10.3.2. Subject Management (adapted from algorithms developed and used in the LookAhead Study [32])

During periods of weight loss, subjects who are taking sulfonylureas, repaglinide or nateglinide may need reductions in diabetes medication(s) to reduce their risk of hypoglycemia.

Each diabetic subject should have a treating physician identified for managing subject's diabetic medication during the study. The treating physician maybe the site PI, site clinical staff, or a treating physician not on the study team, in which case the study site will work collaboratively with the subject's non-study treating physician in managing their risks. The treating physician will be responsible for diabetes medication adjustment while the need for medication reduction may be identified by the study subject, research staff, or individual delivering the lifestyle modification intervention.

At the screening visit, subjects who are taking sulfonylureas, repaglinide or nateglinide will be identified by the site. If non-study treating physicians will be responsible for medication adjustment, they will be contacted by the site regarding the plan for glycemic control during the study. Evidence of the treating physician's acknowledgement on a subject's participation in the study will be obtained before a subject's enrollment in the study.

The definition of hypoglycemic episodes can be found in Appendix A. Study subjects or study staff may identify these episodes.

Hypoglycemic Decision Point is defined as one episode of severe hypoglycemia or non-severe hypoglycemia occurring greater than twice weekly. If a Hypoglycemic Decision Point should occur in a study subject, this, should prompt reassessment of the anti-diabetic regimen and reduction or discontinuation of anti-diabetic medications. Before medication changes are made, judgment should be used in determining whether exceptional and/or alterable circumstances are responsible for the low glucose levels (e.g., hypoglycemia attributable to missing a meal or an unusual degree of physical exercise).

10.3.2.1. Prior to Index Procedure

Prior to the start of the study, subjects treated with sulfonylureas, repaglinide or nateglinide medications will be asked to start monitoring blood glucose (BG) at least twice daily (pre-breakfast and pre-supper). After at least one week of BG measurements have been collected, the BG data will be reviewed and used to make decisions on pre-emptively reducing anti-diabetic medication according to the scheme below (**Figure 14**).

Figure 14. [redacted]

The above algorithm provides general guidelines for adjustments in doses of sulfonylureas, repaglinide and nateglinide, because of the risk of hypoglycemia associated with their use. The exact adjustments in doses of these medications and also a decision on whether the doses of other anti-diabetic medications should be reduced for individual subjects should be determined by the subject's managing physician based on the overall profile of blood glucose levels, with the goal of reducing the risk of hypoglycemia.

10.3.2.2. During Study Follow up

Self-monitoring of blood glucose should be performed twice daily for subjects on sulfonylureas, repaglinide and nateglinide medications during the first 4 weeks after the index procedure, and one week before each scheduled visit. For subjects on other anti-diabetic medications, self-monitoring of BG should be performed during the first week after the procedure. Subjects also will be encouraged to measure BG levels at any time that symptoms suggestive of hypoglycemia occur. Additionally, subjects will be asked to promptly report

documented or suspected episodes of hypoglycemia to the site staff. Subjects will be referred to the treating physician for medication dose adjustment if they experience one episode of severe hypoglycemia or episodes of non-severe hypoglycemia >2 times per week. Guidelines for medication dose adjustment are provided below (Figure 15).

The process of reviewing BG records by study staff or treating physician should continue until the blood glucose records satisfy the following criteria:

(1) no ongoing episode of severe hypoglycemia,

(2) episodes of non-severe hypoglycemia occurring no more often than two times per week, and

(3) No blood glucose values less than 100 mg/dL.

If the risk of hypoglycemia has not been adequately reduced, doses of sulfonulureas, repaglinide, nateglinide, or possibly other anti-diabetic medication(s) should be further reduced or discontinued if appropriate and in the clinical judgment of the subject's treating physician.

In the event of severe hypoglycemia, study staff will document these episodes on the Adverse Event form.

Figure 15. [redacted]

10.4. Managing Hyperglycemia Risks in Diabetic Subjects

Although hyperglycemia is not anticipated as a consequence of the device, some subjects may develop uncontrolled hyperglycemia in the course of the study (e.g., as a result of progression of their diabetes or an intercurrent illness). Signs or symptoms of acute metabolic deterioration, or presence of serious intercurrent illness or trauma should lead to prompt subject evaluation. Responses may include close follow up, adjustment of anti-diabetic medication or diet, or hospitalization. Subjects who require insulin treatment for greater than 14 consecutive days should terminate study participation and have the study device removed.

10.5. Early Device Removal

Early device removal should be considered in the following situations:

- Subject experiences abdominal pain and the pain does not resolve in 5-7 days, in combination with ulcer observation
- Subject has signs of ulcer progression:
  - Enlargement of peptic ulcer by greater than or equal to 25% in length or width over 8 weeks and with a minimum width (short axis) of 1 cm
  - Bleeding, Hgb drops ≥2 g/dL
  - Developing upper abdominal pain, which does not resolve on medical therapy
- Subject has an ulcer size of ≥2cm in diameter or width (the smaller measurement between the length and width), OR ≥ 3cm x 1cm not responding to medication
- Subject requires insulin treatment for greater than 14 consecutive days
- Subject loses ≥ 20% of his/her total body weight in any four-week post-placement period
- Subject achieves a BMI of ≤ 22 kg/m^2 for two consecutive visits before the 12-months follow up
- Subject becomes pregnant

Device removal should be performed according to the device removal procedure described in Section 11.9.10.1 and in the IFU.

To ensure that both study groups are treated the same in a sham-controlled study, the control subjects will be treated as if he/she has received the device. For example, if a control subject has lost ≥ 20% of his/her total body weight in any four-week period during follow up, the subject will exit the study as if he/she will have the device removed.

11. STUDY EVALUATION AND TREATMENT PROCEDURES

11.1. Demographics

A self-reported demographic questionnaire will be administered at baseline to assess subject characteristics that include age, race/ethnicity, psychological health status, and health insurance status.

11.2. Medical History and Concomitant Medication

Subject medical conditions and medication usage will be reviewed, assessed, and documented at each study visit.

11.3. Measurement of Weight, Body Circumference and Calculation of Body Mass Index (BMI)

When the subject is weighed, s/he should be wearing only undergarments and an exam gown.

The weight will be measured in duplicate at each visit. If the two readings are discrepant, it should be repeated until two consecutive identical readings are obtained.

Height will be measured and recorded at the screening visit.

The BMI is calculated to one decimal place, using the subject's weight at each visit and the height value obtained at baseline. A BMI calculator is provided in Appendix D.

Body circumference measures will be performed with the subject standing feet together. The following circumference measurements will be made:

- Hip: measured at the widest part of the hips
- Waist: measured midway between the lowest rib and the iliac crest
- Chest: measured at the 4th intercostal space in the mid-clavicular line
- Neck: measured at the widest part of the neck

11.4. Biochemical Measurements

Fasting blood samples will be obtained at the screening and baseline visits, and at the 6- and 12-month follow-up visits. The following analyses will be performed:

- CBC (Complete blood count), including differential (screen and baseline visits only)
- Chemistry Panel 20 (screen and baseline visits only)
- Lipid levels and lipoproteins (triglycerides, LDL-C, HDL-C, and total cholesterol)
- Glucose, insulin, HbA1c
- High sensitivity C-reactive protein

11.5. Satiety Assessment

Visual analogue scales by Control of Eating Questionnaire (Appendix H) will be used to assess the subject's hunger, fullness, cravings and related dimensions of appetite. [33] The Eating Inventory (Appendix I) will be used to assess cognitive restraint, disinhibition, and hunger. These instruments will be administered at the baseline, 1 week, and 1, 6, 12 month(s) visits.

11.6. Patient Health Questionnaire 9 (PHQ-9)

The Patient Health Questionnaire 9 (PHQ-9) is to be used to assess the subject's level of depression prior to participation in the study. If the subject's score is ≥10, s/he will not be enrolled into the study.

A sample of the PHQ-9 is provided in Appendix E.

11.7. Impact of Weight on Quality of Life (IWQOL– Lite)[34]

The IWQOL-Lite is a subject-completed 31-item instrument that reliably measures how a subject's weight affects his/her quality of life in the five domains of physical function, self-esteem, sexual life, public distress, and work. The IWQOL–Lite will be collected at baseline and at the 6- and 12-month follow-up visits.

A sample of the IWQOL-Lite is provided in Appendix F.

11.8. Test for Helicobacter Pylori

A negative stool antigen test for *H. pylori* is required for study inclusion. The subject should be off antibiotics, antacids, and bismuth for 2 weeks, and not be bleeding before the testing. If the test reveals the subject is positive for *H. pylori*, the subject will be treated accordingly. If a stool retest is negative following completion of the treatment, the subject may be entered into the study. If, after treatment, the subject tests positive for *H. pylori* at the retest, s/he is to be excluded from the study.

11.9. Visit Schedules

The table in Appendix B provides an overview of the schedule of exams and procedures for the study.

11.9.1. Screening Visit (Within 8 Weeks Prior to the Index Procedure)

At the screening visit, the following procedures/assessments will be performed to determine subject eligibility:

- Informed consent prior to the conduct of any study-related procedures
- Demographics (ethnicity, age, gender, education, marital status)
- Medical history, especially the assessment of risk factors and morbidities related to obesity and age when subject first noticed obesity
- Concomitant medications
- Physical examination
- Body mass assessment (body weight, height, calculation of BMI, and measurement of circumferences)
- Patient Health Questionnaire (PHQ-9)
- Behavioral evaluation by registered dietitian, behavioral specialist, or mental health professional
- Urine pregnancy test for females capable of becoming pregnant
- Stool test for *H. pylori*
- Blood tests
    - CBC with differential
    - Chemistry panel 20
    - Fasting lipid panel
    - Fasting blood glucose, insulin, HbA1c, C-reactive protein
- EKG
- Assessment of enrollment eligibility (inclusion/general exclusion criteria)

Each subject will be assessed for suitability to participate in the study by the site Investigator.

Subjects who meet all the inclusion criteria but none of the exclusion criteria will be scheduled for a baseline visit.

11.9.2. Baseline Visit (Within One Week Prior to the Index Procedure)

The following evaluations/procedures are to be performed within 7 days prior to the index procedure:

- Abbreviated physical examination including vital signs (temperature, systolic/diastolic blood pressure, respiration rate, heart rate)
- Body mass assessment (body weight, calculation of BMI, and measurement of circumferences)
- Concomitant medications
- IWQOL-Lite assessment
- Eating Inventory assessment
- Visual Analog Scale assessment
- Urine pregnancy test for females capable of becoming pregnant
- Blood tests
    - CBC with differential
    - Chemistry panel 20
    - Lipid levels and lipoproteins,
    - Glucose, insulin, HbA1c, high sensitivity C-reactive protein
- Assessment for eligibility
- Brief lifestyle counseling according to Appendix C, including recommendation and instruction to follow the caloric target of 1200-1500 kcal/day for subjects ≤ 114 kg (≤ 250 lb) and 1500-1800 kcal/day for subjects > 114 kg (> 250 lb)

If the subject is no longer eligible for the study due to a change in the subject's condition, such as pregnancy, abnormal blood test values, or weight change resulting in a BMI outside of the protocol range, the subject will be excluded from the study and documented as a screen failure.

This visit is not required in subjects whose screening visits and tests are performed within 7 days of the index procedure. In this case, data collected from the screening visit will serve as baseline data.

11.9.3. Index Procedure (Day 0)

The TPS placement procedure will be performed under general or monitored anesthesia care (MAC). Eligible subjects will undergo standard preparation for an endoscopic procedure, followed by an endoscopic assessment of the esophagus, stomach, antrum, pylorus and duodenum. Subjects who meet the endoscopic exclusion criteria will be considered an endoscopic screening failure and excluded from the study.

Subjects who do not possess any endoscopic exclusion criteria will be randomized into Treatment or Control group using a web-based randomization system provided by the study data management organization. Procedure details can be found in the instruction for use (IFU). In brief, a TPSS Access Sheath is inserted over the gastroscope using standard techniques to position the distal tip approximately 6 cm below the gastroesophageal junction. Endoscopic visualization is used to monitor inflation of the distal positioning balloon on the Access Sheath and confirm final insertion position. After removal of the gastroscope and obturator, the TPS Delivery Device is lubricated and inserted into the Access Sheath until fully-seated with the connectors engaged. The TPS Delivery Device is placed on the TPSS Stand and connected to the insufflation system. Deployment of the TPS is accomplished by forward rotation of TPS Advance Torque Knob on the delivery device handle. Following actuation of the TPS locking mechanisms on the TPS Delivery Device, the formed TPS is released into the stomach and the Access Sheath and TPS Delivery Device are withdrawn from the patient. A final endoscopic evaluation is performed to inspect the final device configuration and assess the gastroesophageal tissues prior to completion of the procedure.

In the Control subject, the sham procedure consists of anesthesia and the TPSS Access Sheath placement but no TPS delivery. Effort will be made so that the overall sham procedure time is similar to the TPS placement procedure time.

Subject will be discharged when the site and physician's discharge criteria are met (if designated by the hospital policy and procedures).

Before the subject is discharged, s/he is to be provided with a subject information card. This card provides the phone number and name of the person to contact in case s/he needs medical attention related to the therapy. Additionally, the subject can provide this card to an emergency room doctor, allowing them to contact the Primary Investigator and obtain information about the study. A sample of the card is provided in Appendix G.

The subject should be placed on a liquid diet for 3 days, followed by soft food for a week, slowly returning to normal food in 10 days.

The following procedures/assessments will be performed during this visit:

- Abbreviated physical examination including vital signs (temperature, systolic/diastolic blood pressure, respiration rate, heart rate)
- Body mass assessment (body weight, calculation of BMI, and measurement of circumferences)
- Assessment of medications
- Endoscopic assessment
- Confirmation of eligibility
- TPS placement procedure

- Assessment of AEs that occurred during the procedure

Post-Procedure Follow-Up Visits

Post-procedure follow-up visits are summarized in Appendix B. They include:

- Office visits at 1 week, and 1, 2, 4, 6, 9, 12 months
- Endoscopic assessments at 2, 6, and 12 months
- Visual Analog Scale assessment at 1 week and 1, 6, and 12 month(s)
- Eating Inventory assessment at 1 week and 1, 6 and 12 month(s)
- Blood tests at 6 and 12 months
- IWQOL-Lite at 6 and 12 months
- Device removal at 12 months
- AE assessments at each follow-up visit
- Brief lifestyle counseling at each follow-up visit and brief telephone calls at 7, 8, 10, and 11 months.

11.9.4. One Week Post-Index Procedure (7 ± 2 Days)

The following data are to be collected:

- Abbreviated physical examination (temperature, systolic/diastolic blood pressure, respiration rate, heart rate)
- Body mass assessment (body weight, calculation of BMI, and measurement of circumferences)
- Visual Analog Scale assessment
- Eating Inventory assessment
- Concomitant medications
- Assessment of AEs that occurred since the last visit
- Assessment of blinding
- Brief lifestyle counseling, with specific instruction for participants to transition from a diet of soft foods to a balanced diet of regular foods and calorie target specific to their weight range as described in Section 11.9.2

11.9.5. One Month Post-Index Procedure (30 ± 7 Days)

The following data are to be collected:

- Abbreviated physical examination (temperature, systolic/diastolic blood pressure, respiration rate, heart rate)
- Body mass assessment (body weight, calculation of BMI, and measurement of circumferences)
- Visual Analog Scale assessment
- Eating Inventory assessment
- Concomitant medications
- Assessment of AEs that occurred since the last visit
- Brief lifestyle counseling

11.9.6. Two-Month Post-Index Procedure (60 ± 14 Days)

The following data are to be collected:

- Abbreviated physical examination (temperature, systolic/diastolic blood pressure, respiration rate, heart rate)

- Body mass assessment (body weight, calculation of BMI, and measurement of circumferences)
- Concomitant medications
- [redacted]
- Assessment of AEs that occurred since the last visit
- Brief lifestyle counseling

11.9.7. Four-Month Post-Index Procedure (120 ± 14 Days)

The following data are to be collected:

- Abbreviated physical examination (temperature, systolic/diastolic blood pressure, respiration rate, heart rate)
- Body mass assessment (body weight, calculation of BMI, and measurement of circumferences)
- Concomitant medications
- Assessment of AEs that occurred since the last visit
- Brief lifestyle counseling

11.9.8. Six-Month Post-Index Procedure (180 ± 14 Days)

The following data are to be collected:

- Abbreviated physical examination (temperature, systolic/diastolic blood pressure, respiration rate, heart rate)
- Body mass assessment (body weight, calculation of BMI, and measurement of circumferences)
- Concomitant medications
- IWQOL-Lite
- Visual Analog Scale assessment
- Eating Inventory assessment
- Blood tests (lipid levels and lipoproteins, glucose, insulin, HbA1c, high sensitivity C-reactive protein)
- [redacted]
- Assessment of AEs that occurred since the last visit
- Brief lifestyle counseling

11.9.9. Nine-Month Post-Index Procedure (270 ± 21 Days)

The following data are to be collected:

- Abbreviated physical examination (temperature, systolic/diastolic blood pressure, respiration rate, heart rate)
- Body mass assessment (body weight, calculation of BMI, and measurement of circumferences)
- Concomitant medications
- Assessment of AEs that occurred since the last visit
- Brief lifestyle counseling

11.9.10. Twelve-Month Post-Index Procedure (365 ± 30 Days)

The following data are to be collected:

- Physical examination

- Body mass assessment (body weight, calculation of BMI, and measurement of circumferences)
- Concomitant medications
- IWQOL-Lite
- Visual Analog Scale assessment
- Eating Inventory assessment
- Blood tests (lipid levels and lipoproteins, glucose, insulin, HbA1c, high sensitivity C-reactive protein)
- Endoscopic assessment
- Assessment of AEs that occurred since the last visit
- Assessment of blinding
- Brief lifestyle counseling
- Unblinding and Pivotal study exit

The above data are to be collected prior to unblinding with the exception of the endoscopic assessment, which is to be collected at the time of removal.

Subjects who were assigned to the Control group will not require an endoscopy at this visit since device removal is unnecessary but they should remain blinded until the all other data are collected.

11.9.10.1. TPS Device Removal

The TPS is to be removed 365 ± 30 days after the index procedure under general or MAC anesthesia. An endoscopic assessment will be performed in all subjects followed by TPS removal in the Treatment group. The device removal procedure is described in detail in the IFU [redacted]

Subjects will be discharged according to the hospital and physician's discharge criteria.

All procedure- and device-related AEs must be followed until resolution or stabilization (the Investigator does not expect any further improvement or worsening of the event). Following study exit, follow-up will be according to clinical practice.

Subjects will be informed that his/her participation in this study is complete. The subject's study exit will be documented.

11.9.11. Unscheduled Visit

If a subject is hospitalized, seen in the emergency room, or has an unscheduled clinic visit, efforts should be made to collect the following data:

- Relevant medical history, physical examination, and laboratory testing findings
- Concomitant medications
- Assessment of AEs

These assessments should be documented on the eCRFs as appropriate.

11.9.12. Telephone Contact at Months 7 (210±7 days), 8 (240±7 days), 10 (300±7 days), and 11 (330-14 days)

In Months 7, 8, 10, and 11, subjects will be contacted by telephone by study personnel(s) who deliver(s) the lifestyle interventions. The subject and study personnel will have a brief (15-minute) telephone calls. During these calls, subjects will report on changes in weight, dietary intake, eating behavior, and physical activity level. These telephone calls are designed to promote adherence to the lifestyle modification protocol. The provider will reinforce positive behaviors consistent with the lifestyle modification program and problem solve issues related to weight gain, increased caloric intake or decreases in physical activity.

12. ASSESSMENT OF SAFETY

Safety will be evaluated through a risk-benefit assessment of the adverse events profile compared to the efficacy demonstrated by the TPS treatment. The incidence of Adverse Events (AEs), Serious AEs (SAEs), Serious Adverse Device Effects (SADEs), and Unanticipated Serious Adverse Device Effects (UADEs) will be captured.

12.1. Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject that occurs during any part of the clinical study, whether related to the investigational device or not. Pre-existing conditions are not reported as AEs unless there has been a worsening in severity or frequency which cannot be attributed to the disease's natural history or progression. Protocol-defined follow-up visits and pre-scheduled endoscopies (including device placement/removal, patient surveillance, and planned diagnostic endoscopies) are not considered adverse events.

For AEs, the event description, severity, date of onset, treatment, outcome, and relationship to device will be collected on the AE eCRF.

All procedure- and device-related AEs must be followed until resolution or stabilization (the Investigator does not expect any further improvement or worsening of the event).

An Adverse Device Effect (ADE) is any adverse event that is considered possibly-related or related to the device. An ADE may occur at any time after exposure to the investigational device.

Determination of whether there is a reasonable possibility that the investigational device caused or contributed to an AE will be reported by the Investigator and reviewed by the CEC as described in Section 12.2.

Determination will be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease, and presence (or absence) of more-likely cause.

12.1.1. Serious Adverse Event

A SAE is an 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
    - requires 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

Here, "life-threatening" refers to an event when the patient is at substantial risk of dying at the time of the adverse event, it does not refer to an event that hypothetically might have caused death if it were more severe; "permanent" is defined as irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

For the purpose of this study, endoscopic observations managed by medication and endoscopic surveillance as described in Guidelines for Managing Endoscopic Observations (Section 10.2.2) are not considered as SAEs. Diagnostic endoscopy is not considered as "intervention" in the context of SAE. Planned hospitalization for a pre-existing condition is not considered as a SAE.

12.1.2. Serious Adverse Device Effect

An SADE is a SAE that is possibly related or related to the device.

12.1.3. Unanticipated Adverse Device Effects

Unanticipated adverse device effects (UADE) are any serious adverse device effects on health or safety or any life-threatening problem or death caused by, or associated with, the investigational study device if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including IFU) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

When an AE meets the definition of a UADE or that relationship is unknown, the Investigator will report the event to BARONova within 24 hours but no later than 10 working days after the Investigator first learns of the effect and reports to the reviewing IRB as required.

12.2. Device Relationship (Causality)

Causality assessment is required for AEs (and SAEs) that occur during clinical investigations. There is currently no standard international nomenclature to describe the degree of causality or relatedness of an AE with the Investigational Device (ICH, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, 1994). The following terms will be used during this study:

- Related - An AE that is directly and clearly related to the Investigational Device;
- Possibly Related - There is a reasonable likelihood that the event is due to the Investigational Device, as evidenced by the following:
    - There may be temporal association with the Investigational Device (e.g., within 24 hours of device placement)

- The event, or level of severity of the event, is unlikely to be explained by other etiologies (known to be related to the study disease, subject's baseline medical condition, or concomitant medication)

- Unlikely Related - The AE is not temporally related to the Investigational Device, or is known to be related to one of the following:
  - Morbidity associated with underlying medical condition
  - Anesthesia
  - Upper GI endoscopy
  - Concomitant medication
  - A relationship to the Investigational Device is not biologically plausible
- Not related - The AE is definitely not related to the Investigational Device

12.3. Adverse Event Reporting

12.3.1. Sponsor Reporting Requirements

The Sponsor will conduct an evaluation of any reported UADEs and will report the results of this evaluation to the FDA, IRBs, and participating Investigators within 10 working days after first receiving notice of the event

12.3.2. Clinical Site Reporting Requirements

- All AEs and ADEs will be recorded by the Investigator or designee on the eCRFs provided
- Any SAEs are to be reported to the Sponsor within 36 hours except UADE or suspected UADE which is to be reported within 24 hours of knowledge of the event, followed by a written confirmation by the Investigator within 5 working days
- The Investigator at each site is ultimately responsible for reporting AEs , SAEs and UADEs to the IRB according to local IRB requirements

13. CLINICAL EVENT COMMITTEE

An independent Clinical Events Committee will be formed to review and adjudicate clinical adverse events. The committee will be comprised of physicians who will not participate in the enrollment or treatment of subjects in this study.

Events to be reviewed by this committee will be defined in the CEC charter. Any event listed in the CEC charter that is reported in an eCRF may result in the acquisition of relevant explanatory or supportive documents, which may include source documents from the hospital, as needed. Copies of these documents will be distributed to members of the CEC. The CEC will be blinded to subject's treatment whenever possible. When evaluating the device relationship of an event, the CEC will treat the subject as if he/she is in the treatment group.

The interpretation of the event as classified and adjudicated by the CEC will be used in the final safety analyses.

14. DATA SAFETY MONITORING BOARD

The DSMB is composed of independent physicians and a biostatistician who are not participating in the study and will not be affiliated with BARONova, the Investigators, or the investigational sites. The DSMB has access to unmasked data, will review the study on a periodic basis, is responsible for making recommendations regarding any safety or compliance issues throughout the course of the study and may recommend to the Steering Committee to modify or stop the study. However, all final decisions regarding study modifications or study termination rest with the Steering Committee.

All cumulative safety data will be reported to the DSMB and reviewed on an ongoing basis throughout enrollment and follow-up periods to ensure subject safety. Every effort will be made to allow the DSMB to conduct an unbiased review of subject safety information. All DSMB reports will be made available to the FDA upon request but will otherwise remain strictly confidential.

DSMB will meet according to the following schedule:

a. Initial meeting will commence before the study start or shortly after the study start

b. DSMB will convene as often as necessary but at a minimum twice a year during enrollment phase, with the first review meeting occur within the first six months of enrollment or no later than the first 45 subjects have completed the 1-month follow up visit. If the enrollment dynamic changes, the Sponsor may increase or decrease the frequency of the meeting

c. DSMB meeting will be convened if the staged safety monitoring threshold has been exceeded as described in Section 5.4 and Section 15.5.6.

d. Additionally, a DSMB meeting may be requested by DSMB member, the Sponsor, IRB, or the Study Steering Committee at any time to discuss safety concerns if it arises.

In the case that a DSMB meeting is triggered by the staged safety monitoring threshold, the DSMB will review the data and provide recommendation to the Sponsor within 15 days. Based upon DSMB recommendation, Sponsor will implement necessary actions which may range from continuous monitoring, protocol modification, stopping of enrollment to device removal. Sponsor will inform FDA about the course of action following the DSMB review as described in Section 5.4.

15. STATISTICAL DESIGN AND ANALYSIS

15.1. Statistical Overview

Data will be summarized by the number, mean, median, standard deviation and range for continuous variables and by number and relative frequency for categorical variables. Summaries will be presented by treatment group and visit as appropriate. A summary of the subjects combined will be provided for the baseline information only. Missing data imputation approaches are outlined below.

The alpha level will be set to 0.05 based on the two-sided testing and 0.025 for the one-sided approach, if not explicitly stated otherwise. Study success criteria are defined in Section 15.3.1. Statistical testing and confidence intervals for sensitivity analyses and secondary endpoints will be presented as an aid in interpreting study results, but statistical significance is not required for study success. Unless otherwise indicated, all statistical inferences will be based on two-sided 95% confidence intervals and p-values less than or equal to 0.05 will be considered significant.

15.2. Analysis Populations

The following analysis populations are defined for the study: Intent-to-Treat (ITT), modified Intent-to-Treat (mITT), Per-Protocol (PP) and Completed Cases (CC). The primary effectiveness hypotheses will be tested on the PP population. The primary safety analysis will be performed on mITT population. The ITT and CC populations will be used in a sensitivity analysis of the primary effectiveness endpoint.

- Intent-to-Treat: The Intent-to-Treat population includes all randomized and enrolled subjects as defined in Section 7.4 regardless of whether or not the subject received the randomized treatment.
- Per-Protocol: The Per-Protocol population is a subset of the ITT population and includes all subjects who receive the assigned treatment and do not have any major eligibility violations.

- Modified Intent-to-Treat: The mITT population consists of the ITT population subjects who received the assigned treatment and that have at least one post-treatment follow-up, including the index procedure visit.
- Completed Cases: The CC population includes all enrolled subjects who have the 12-month follow-up visit, or have completed the study based on reaching the BMI objective of ≤ 22 kg / m^2 in two consecutive follow-up visits as described in Section 5.1.

15.3. Study Objectives and Hypotheses

15.3.1. Primary Effectiveness Objective

The primary objective of this study is to assess the clinical effectiveness of the BARONova TransPyloric Shuttle for weight reduction in patients with obesity, with a BMI of 35.0 to 40.0 kg/m^2, or a BMI of 30.0 through 34.9 kg/m^2 with one or more obesity-related comorbid conditions over the 12 months treatment period.

The hypothesis associated with the first co-primary endpoint is that the subjects in the Treatment group will have superior weight loss in %TBL compared to subjects in the Control group at 12-month follow up. The statistical null and alternative hypothesizes are:

$$H_{i0}: \mu_T - \mu_C \leq \delta \text{ vs.}$$
$$H_{iA}: \mu_T - \mu_C > \delta,$$

Where,

μ_T is the mean % TBL at 12 months in the treated group

μ_C is the mean % TBL in the control group at 12 months.

δ is the superiority margin.

The hypotheses will be tested using a one-sided two-sample t-test for independent samples at the alpha level of 0.025. If the test value exceeds the nominal critical point, the H0 will be rejected. The testing may be performed using mixed model repeated measurements approach. If the mixed model is used, the decision about the rejection of null hypothesis will be based upon the test for the 12-month follow-up outcomes. The primary statistical test will use $\delta = 0$. If the H0 is rejected, the 95% confidence interval for the difference in %TBL between the groups will be created. The lower limit of the interval is the statistically achieved superiority margin.

The second co-primary effectiveness endpoint is the percentage of Treatment subjects with a ≥ 5% TBL at 12 months. Proportion of subjects who lose at least 5% of their baseline weight will be compared against the target proportion of 50% using a one-sided test for hypothesized population proportion.

The statistical null and alternative hypotheses are:

$$H_{ii0}: p_T < \Pi_0 \text{ vs.}$$
$$H_{iiA}: p_T \geq \Pi_0,$$

Where,

p_T is the proportion in the study subjects from the Treatment group

Π_0 is the reference proportion (i.e 0.5 (50%))

Study statistical success is achieved if study null hypotheses for both co-primary endpoints are rejected. FDA recommends that the H_{i0} is rejected with superiority margin $\delta = 5\%$ and the H_{ii0} is rejected.

15.3.2. Safety Objective

The objective of the safety analysis is to provide safety information sufficient to characterize and summarize adverse events observed during the study.

15.4. Sample Size Considerations

A total sample size of 270 subjects is planned for the pivotal study cohort. The ENDObesity I study provided estimates for the mean %TBL of 14.5 (SD=5.8) at 6 months of follow-up. For the purposes of the sample size calculation, the assumed means were 13% in Treatment and 5% in Control subjects. This provides a difference (Treatment – Sham Control) in mean %TBL of 8% and the assumed standard deviation was increased to 9% (approximately 1.5 times that observed in the ENDObesity I study) to account for a more conservative estimate of the standard deviation. Under these assumptions, a sample size of 243 subjects (162 Treatment, 81 Control) has 90% power to reject H_0 under the 4% superiority margin scenario and 68.4% power under the superiority margin of 5%. Under less conservative scenario of standard deviation of 7, the study has 88% power to reject H_0 under the 5% superiority margin scenario and 99% power under the 4% superiority margin. The study will enroll 270 subjects (approximately 180 in the Treatment groups and 90 in the Control group) to compensate for losses to follow-up.

The second co-primary endpoint is to demonstrate the proportion of subjects with a $\geq$ 5% TBL at 12 months is greater than 50%. Under the assumption of 65% responder rate in the Treatment group, the study requires 113 treatment subjects in order to have 90% power to reject null hypothesis for the second co-primary endpoint.

A third consideration for the sample size is the ability to provide reasonable safety data from the study. With the proposed sample size of 180 subjects in the Treatment group, there is an 80% likelihood to observe at least one event of any specific complication if it occurs in at a rate of 0.9% or greater in subjects treated with the TPSS. The upper limit of 95% exact binomial confidence interval for an event rate if none of 180 subjects has specific complication is 2.0%.

15.5. Statistical Analysis

15.5.1. Accountability and Demographics

The number of subjects in each population will be summarized overall and by site for each treatment group. In addition, the number of subjects completing the study and withdrawing from the study will be presented along with reasons for withdrawal.

Descriptive summaries for baseline and demographic characteristics including age, gender, height, weight, baseline BMI, medical history, and co-morbidities will be presented by treatment group.

15.5.2. Comparability of the Treatment Groups

The demographic and prognostic variables measured at study entry will be compared between the Treatment and the Control groups. Continuous variables will be compared with Student t-test for two independent samples or Wilcoxon rank sum test, and categorical variables will be compared with Fisher's exact test or Chi-square test.

15.5.3. Primary Analysis

The %TBL will be calculated as $(\text{Weight(kg)}_{BL} - \text{Weight(kg)}_{FUP})/\text{Weight(kg)}_{BL}$. Where Weight(kg)_{BL} is the subject's weight at baseline in kilograms and Weight(kg)_{FUP} is the subject's weight at follow-up in kilograms.

The %TBL will be summarized at each follow-up visit through 12 months along with the observed total body weight at baseline and each follow-up visit by treatment group.

The testing of null hypotheses for the co-primary efficacy endpoints is described in Section 15.3.1.

In order to accommodate missing data in the primary effectiveness analyses, a multiple imputation approach will be used to impute missing follow-up weight observations. A total of 5 imputed samples will be created. Covariates (e.g., gender) will be used in the imputation procedure in addition to the subject's weight from previous visits. The multiple imputation approach was first described by Rubin.[35] The SAS procedures MI and MIANALYZE will be used to create the imputations and perform the analysis. The statistical null hypotheses for both co-primary endpoints will be tested on multiply imputed data sets. Sensitivity analyses will be done by evaluating the primary analysis on the ITT and CC cohorts. Further, a last observation carry forward (LOCF) imputation will be performed for the sensitivity purposes.

Additionally, the %TBL median, mean and standard deviation and percent of subjects with greater than 5%TBL will be summarized by treatment group and levels of covariates. Covariates include gender (male versus female), race (Caucasian versus non-Caucasian), age (≤ median, > median), and baseline BMI (30-34.9 kg/m^2 and 35-40.0 kg/m^2).

15.5.4. Secondary Analysis

Secondary endpoints will be summarized by treatment group for the ITT and per-protocol cohorts based on the observed data and include the following summaries:

- Proportion of subjects achieving at least 7% and 10% TBL at 12 months;
- Percent TBL at 1 week, 1, 2, 4, 6, 9 and 12 months in the Treatment versus Control group;
- Percent EWL at 1 week, 1, 2, 4, 6, 9 and 12 months in the Treatment versus Control group;
- Proportion of subjects who achieve at least one obesity class reduction at 1 week, 1, 2, 4, 6, 9 and 12 months in the Treatment versus Control group;
- Change of BMI at 1 week, 1, 2, 4, 6, 9 and 12 months from baseline in the Treatment versus Control group;
- Change in weight-related quality of life at 1 week, 1, 2, 4, 6, 9 and 12 months as assessed by IWQOL-Lite Questionnaire in the Treatment versus Control group;
- Change in eating behavior at 1 week, 1 month and 12 months as assessed by the Eating Inventory;
- Change in appetite, hunger and fullness at 1 week, 1 month, 6 and 12 months as assessed by Visual Analog Scales in the Treatment versus Control group;
- Change in comorbid conditions and selected clinical parameters at 6 and 12 months in the Treatment group:
    - Prevalence of the metabolic syndrome and its individual components
    - Glucose, insulin, and insulin resistance (as estimated by HOMA)
    - High sensitivity C-reactive protein (hsCRP)
    - Lipid levels (LDL-C, HDL-C, and triglycerides)
    - Blood pressure
    - Waist circumference

The analysis of total body weight loss is described above. The other continuous and binary variables will be summarized descriptively by visit with 95% CIs presented for the mean values and proportions, respectively. For continuous endpoints, the change from baseline will be calculated if appropriate, and a t-test or a sign-rank test used to evaluate the null hypothesis that the change from baseline is centered around 0 (no change) within each treatment group. Treatment group comparisons for continuous endpoints will be made using mixed

models with post-hoc tests for each follow-up, and comparisons for qualitative variables will be made using Fisher's exact test, McNemar test or chi-square test, as appropriate.

The percent excess weight loss (%EWL) will be calculated as $(Weight(kg)_{BL} - Weight(kg)_{FUP})/ ExcessWeight(kg)_{BL}$ where $ExcessWeight(kg)_{BL}$ is calculated as difference between the subject's baseline weight in kilograms and the kilograms at which the subject's BMI would be 25.

15.5.5. Safety Analysis

The safety analyses will be performed using the mITT Population.

An overall summary of AEs will be provided including the number of events and percent of subjects with any AEs, SAEs, and UADEs. For each type of event, the number of events and number and percent of subjects with the event will be provided in a table. Separate summaries of all adverse events will be summarized by relationship to device and procedure. Adverse events will be coded using MedDRA medical dictionary.

15.5.6. [redacted]

[redacted]

[redacted]

15.5.7. [redacted]

[redacted]

15.5.8. Assessment of Poolability

The poolability of the study results across study sites will be assessed. A regression model with covariates for study site, treatment group, and site*treatment interaction will be fit. Study sites with fewer than 10 subjects will be combined into a single pseudo-site for this analysis. If the p-value for the site*treatment interaction term is < 0.10, this will be considered statistical evidence of a potential differential treatment effect by site.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. Selection of Study Sites and Investigators

The Sponsor will select Investigators who are qualified by training and experience to perform clinical research in this field and to participate in the clinical investigation. Sites will be selected based upon an assessment of the qualifications of the Primary Investigator and the facilities at each site. All Investigators will be trained on the device, the protocol and all study procedures prior to enrolling subjects.

A pre-investigation visit will be conducted at each study site to assure that the Investigator and the study staff understand the obligations for using and managing the investigational device, following the study protocol, obtaining informed consent, adhering to FDA and IRB regulations, and conducting clinical research.

16.2. Training

16.2.1. Site Training

All Investigators/study personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Remote over-the-phone or web-based training will take place as necessary. Training of Investigators/study personnel will include, but is not limited to, the investigational plan, participant recruitment, enrollment (including review of inclusion and exclusion criteria), subject retention, investigational device usage, protocol requirements, case report form completion, and study personnel responsibilities. At least one individual at each site also will be trained in the delivery of the lifestyle modification counseling and the behavioral/psychosocial assessment by a consultant with relevant expertise. All Investigators/study personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Investigator/study personnel must not perform any study-related procedures prior to being trained.

Investigators who perform the device placement/removal procedures will be trained on device use. BARONova personnel will provide in-person technical support for a minimum of the first five procedures at each site.

16.2.2. Monitor Training

The Sponsor or designee will engage monitors that are qualified by appropriate training and experience to review the conduct and quality of the study. Prior to working on the study, monitors will be trained to the investigational plan, case report forms, and the device/procedure knowledge. Such training will be documented.

16.3. Study Monitoring

BARONova and/or a designee (e.g., a Contract Research Organization), will monitor the clinical study in a manner consistent with FDA regulations and the Good Clinical Practice (GCP) standards adopted by BARONova.

The Investigator is required to ensure compliance with all procedures required by the Investigational plan and by study procedures provided by the Sponsor. The Investigator agrees to provide reliable data and all information requested by the Investigational Plan including eCRFs, Discrepancy Clarification Forms or other appropriate instrument according to the instructions provided, and to ensure direct access to source documents to Sponsor representatives.

Clinical Monitors will periodically monitor all eCRFs and corresponding source medical records for each subject. The monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of eCRFs, to resolve any inconsistencies in the study records, and to

ensure that all protocol requirements, applicable regulatory regulations, and Investigator's obligations are being fulfilled. Monitoring and data verification may be performed remotely or onsite.

The Investigator and his/her staff will be expected to cooperate with Sponsor's personnel or designee and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information.

16.4. Source Data Verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (e.g., subject files, physician notes, discharge summaries, operative records, study worksheets, etc.). All data reported on the eCRF should be supported by source documents, unless the eCRF also serves as a source document.

16.4.1. Definition of Source Data

Source data includes all information in source documents (original records, certified copies of original records, appointment books, original laboratory records, and original data recorded on customized worksheets) and includes all original recordings or copies of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Certain data may be directly entered into eCRF. In this case, the eCRF serves as source document.

16.5. Direct Access to Source Data/Documents

The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC and regulatory inspection(s).

Consenting subjects are agreeing to allow the Sponsor or designee access and copying rights to pertinent information in their medical records relevant to study participation. As part of the informed consent, the Investigator or designee will obtain permission for regulatory authorities to review any records identifying subjects in this study. Sponsor will not otherwise release any personal information (refer to Section 18.3 Confidentiality).

16.6. Maintain Blinding during the Study

Only the data management organization and the unblinded statistician have access to the randomization code. The Sponsor's study management team, the Study Steering Committee, the CEC, and the statistician who is responsible for study design and data analysis will be blinded to subject's treatment during the study. The monitors from the monitoring organization will have access to subjects' treatment information in order to perform study monitoring and source data verification.

At each site, the Investigator who performs the index procedure and endoscopic follow up will not collect the outcome data. The Investigator or study coordinator who collects outcome data will be masked. Source documents containing subject treatment information will be either masked or access-controlled according to each site's practice. Each site's blinding procedure will be assessed by the study monitors at the monitoring visits.

In exceptional circumstances when knowledge of the Investigational Device is essential for patient safety in case of serious adverse event, the blinding for this subject may be broken.

The Investigator should promptly (within 24 hours) document and explain to the Sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the study subject.

16.7. Protocol Deviations

It is the Investigator's responsibility to ensure that there are no deviations from the protocol except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject. In the event of any deviation from the protocol, a Protocol Deviation Case Report Form will be completed.

The occurrence of protocol deviations will be monitored by the Sponsor for evaluation of Investigator compliance to the protocol, Good Clinical Practice (GCP), and regulatory requirements. The Investigator will inform the IRB of protocol deviations according to requirements of each reviewing IRB.

A protocol deviation for this protocol consists of, but is not limited to, the following:

- Failure to obtain subject's informed consent prior to any study-related activities and the index procedure
- Enrollment of subjects who do not meet all eligibility requirements
- Failure to conduct protocol required clinical follow-ups and within time windows
- Failure to report SAEs/UADEs according to protocol requirements

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions will be advised if necessary and the methods, plan or other activities put in place to ensure non-recurrence will be documented by the Investigator and forwarded to the sponsor or their designee. Continued protocol deviations despite re-education of study site personnel and/or persistent protocol deviations may result in termination of the site's study participation. Subjects already enrolled at these sites will continue to be followed per protocol guidelines.

16.8. Termination of Study Site Participation

The Sponsor reserves the right to stop the enrollment of subjects at a study center at any time during the study. Specific instances that may precipitate terminating a study center may include the following:

- Unsatisfactory subject enrollment
- Failure to comply with protocol
- Failure to obtain informed consent
- Inaccurate and/or incomplete data recording on a recurrent basis
- Failure to report SAEs in timely manner
- Loss of (or unaccounted for) investigational product inventory
- Severe protocol deviations without justification or failure to implement corrective actions

16.9. Study Steering Committee (SSC)

The Steering Committee is composed of Principal Investigators, subject experts, and BARONova's representatives. The Steering Committee has the overall responsibility for producing and conducting a scientifically sound study. In that capacity, the Steering Committee will participate in protocol development and review; address and resolve scientific issues encountered during the study; oversee ongoing study conduct and address operational issues that may warrant a protocol amendment or other corrective action; and recommend corrective actions, including premature termination of the study. The Steering Committee will also oversee the presentation and /or publication aspect of the study.

17. DATA HANDLING AND RECORD KEEPING

For the study duration, the Investigator will maintain complete and accurate documentation including but not limited to the following: medical records, study progress records, laboratory reports, case report forms, signed informed consent forms, device records, and correspondence with the IRB and study monitor/Sponsor, AE reports, and information regarding subject discontinuation or study completion.

17.1. Source Documentation

For the duration of the study, the Investigator shall take responsibility for maintaining complete and accurate source documentation.

The following materials should be included in the patient record:

- Subject medical history/physical condition prior to study involvement
- Dated and signed notes on the day of entry into the study referencing BARONova, the study, subject study ID number, and a statement confirming informed consent
- Dated and signed notes from each subject's visit (for specific results of procedures and exams)
- AEs reported and their outcome including supporting documents
- Subject's condition upon study completion or withdrawal

17.2. Case Report Form Completion

Accurate primary data collection will be performed by site staff trained on the protocol and eCRF completion. All data fields will be completed where appropriate. However, if data are not available (i.e., missed visit, etc.), the site will receive instruction regarding electronic documentation. As data are entered, automated cross-check programs will search for any data discrepancies in the eCRFs. Appropriate error messages will be generated, allowing for the modification and/or verification of the entered data. Queries will generally be sent to the investigational site using an electronic data query system that includes an automated audit trail of the corrections. The Investigator, or designee, will certify that the data are complete and accurate by applying an electronic signature to the eCRF. Any subsequent alterations, corrections, or additions will be reviewed and electronically signed by the Investigator prior to the database lock.

The Sponsor or designee will provide clinical monitoring to include eCRF review and parity checks with the source documentation, including operator worksheets retained with eCRF documentation and health care facility charts.

17.3. Record Retention

The Investigator/Site will maintain all records pertaining to this study for the later of (a) five years following study completion, or (b) five years after FDA notified that the study under the IDE has been terminated by the Sponsor, or (c) as otherwise instructed by the Sponsor. Investigator will be notified by Sponsor of the date of completion or discontinuation of the study.

To comply with these requirements, the Investigator will not dispose of or transfer any records relevant to this study without either (1) written permission from the Sponsor, or (2) providing an opportunity for the Sponsor to archive the records with an external vendor.

18. ETHICAL CONSIDERATIONS

18.1. Institutional Review Board Review

IRB approval for the protocol and informed consent form will be obtained by the Investigator prior to study participation by subjects. The approval letter must be obtained prior to beginning this study and a copy must be provided to the Sponsor. No changes will be made to the protocol or informed consent form without appropriate approval from the IRB, the Sponsor and/or the regulatory agencies. Additionally, the Primary Investigator or representative will provide an IRB membership list or assurance number to the Sponsor or its designee.

As per local IRB requirements, the Investigator will report study progress until it is completed. Further, any protocol amendments as well as associated informed consent changes will be submitted to the IRB and written approval must be obtained prior to implementation.

18.2. Informed Consent

Written informed consent must be obtained prior to any study-related activities and the index procedure.

The Investigator should clearly explain that this is an elective procedure and should discuss the potential risks and benefits associated with participation in this study. Subjects should be advised that the BAROnova TPS should not be considered a lifetime device and must be removed at 12 months post-placement since it has not been tested for such use.

Subjects providing informed consent agree to permit the Sponsor or designee access to pertinent information in their medical records concerning their participation in this study. This confidential patient information may be shared with regulatory agencies as required; however, the Sponsor undertakes not to otherwise release the subject's personal and private health information.

18.3. Confidentiality

The identity of subjects enrolled in the study and the information contained in their study records will be kept confidential by BAROnova. As part of the Investigator training session, Investigators will be instructed in the importance of confidentiality and the techniques for protecting subjects' privacy and rights. Subject's personal information will be handled at all times in accordance with appropriate confidentiality standards and applicable data protection and local privacy laws.

Each subject will be assigned a study identification number to be used on eCRFs and other study records sent to the Sponsor or its designee. Initials will also be used to track study subjects.

Confidentiality will be protected as much as possible throughout the study. Medical records will be reviewed by representatives of BAROnova and/or its designee and will be made available for review as required by the IRB and regulatory authorities. Results of data collected will be reported as statistical information only. The subject's name will not be used or otherwise disclosed unless required by US law or regulation.

19. INVESTIGATIONAL DEVICE MANAGEMENT

19.1. Device Accountability

The Sponsor will only distribute investigational devices to sites that are part of the clinical investigation. The Sponsor will maintain complete, current and accurate records pertaining to the distribution of the investigational devices and follow record keeping requirements in accordance with Good Clinical Practices and FDA Regulations.

The Investigator is responsible for maintenance of adequate records of the receipt, disposition, and/or return of all investigational devices distributed to their site. At study termination, or termination of the site from participation in the study the Sponsor will provide specific instructions to the study sites on unused investigational devices.

Use of the investigational device outside of the protocol (e.g., compassionate use) without prior written approval is strictly forbidden and may constitute grounds for removal of the Investigator/site from the study.

19.2. Device Return

All unused investigational devices, including those unused due to malfunction, device failure, device complaint or device dropped on the floor, must be returned to the Sponsor immediately according to the returned goods process. All devices and/or remaining components that are associated with a device malfunction or clinical procedural failure should be returned to the Sponsor.

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APPENDIX A: DEFINITIONS AND ACRONYMS

1. **ACC**: American College of Cardiology
2. **ADHD**: Attention Deficit Hyperactivity Disorder
3. **Adverse Events (AEs):** Any untoward medical occurrence in a clinical investigation subject that may occur during any part of the clinical study. This definition includes events occurring during the procedure and through the follow-up period whether related to the investigational device or not. Pre-existing conditions are not reported as AEs unless there has been a worsening in severity or frequency which cannot be attributed to the disease's natural history or progression. Protocol-defined follow up visits and pre-scheduled endoscopies (including device placement/removal, patient surveillance and planned diagnostic endoscopies) are not considered adverse events.
4. **Adverse Events Severity:**
    a. **Mild:** Causes no limitation of usual activities, may or may not require treatment and resolves with no permanent consequence.
    b. **Moderate:** Interferes temporarily and causes some limitation of usual activities and most often requires treatment.
    c. **Severe:** Prevents or severely limits usual activities
5. **Adverse Device Effect (ADE)**: An adverse event that is considered possibly-related or related to the device.
6. **AE stabilization**: when the AE (in the investigator's opinion) is not likely to improve or worsen
7. **AHA**: America Heart Association
8. **Anemia**: hemoglobin <11.0 g/dl for female and <12.0 g/dl for male
9. **BG**: Blood Glucose
10. **BIB**: BioEnterics Intragastric Balloon
11. **BMI:** Body Mass Index
12. **CBC:** Complete Blood Count
13. **CEC:** Clinical Event Committee
14. **DSMB**: Data Safety Monitoring Board
15. **eCRFs:** Electronic Case Report Forms
16. **EKG**: Electrocardiogram
17. **Enrolled:** when subject has given written informed consent and the TPSS Access Sheath has been placed in the subject
18. **EWL:** Excess Weight Loss
19. **GBP:** Gastric Bypass
20. **GERD**: Gastroesophageal Reflux Disease
21. **GI:** Gastrointestinal
22. **HbA1c:** Glycated haemoglobin (A1c)
23. **HDL:** High-density lipoprotein

24. **Hgb:** Hemoglobin
25. **HOMA:** Homeostasis Model Assessment.
26. **hsCRP:** High sensitivity C-reactive protein
27. **Hypertension:** arterial blood pressure > 140 mmHg systolic or > 90 mmHg diastolic
28. **(Uncontrolled) hypertension:** systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg
29. **Hypoglycemia Classification** (from the American Diabetes Association).

    a. **Severe hypoglycemia**:

An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

b. **Non-Severe hypoglycemia**:

- ***Documented symptomatic hypoglycemia***: An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than or equal to 70 mg/dL.
- ***Asymptomatic hypoglycemia***: An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL.
- ***Probable symptomatic hypoglycemia***: An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but the event was presumably caused by a measured plasma glucose concentration less than or equal to 70 mg/dL.
- ***Relative hypoglycemia***: An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration greater than 70 mg/dL. This classification subcategory reflects the fact that subjects with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels greater than 70 mg/dL as plasma glucose concentrations decline toward that level.

30. **IFU:** Instructions for Use
31. **Index Procedure:** The TPS placement or sham TPS placement procedure
32. **IRB**: Institutional Review Board
33. **ITT:** Intent to Treat
34. **IWQOL-Lite**: The Impact of Weight on Quality of Life-Lite Questionnaire
35. **K-M**: Kaplan-Meier
36. **LOCF**: Last Observation Carried Forward

37. **MAC:** Monitored Anesthesia Care**,** refers to the anesthesia personnel presenting during a procedure. It includes all aspects of anesthesia care–a pre-procedure visit, intra-procedure care and post-procedure anesthesia management
38. **Metabolic syndrome:** Defined by the presence of at least 3 of the following 5 risk factors according to AHA/NHLBI guideline[36]
    1) Fasting glucose ≥100 mg/dL, or receiving drug therapy for hyperglycemia
    2) Blood pressure ≥130 mm Hg systolic and/or ≥85 mm Hg diastolic, or receiving drug therapy for hypertension
    3) Triglycerides ≥150 mg/d (1.7 mmol/L), or receiving drug therapy for hypertriglyceridemia
    4) HDL-C < 40 mg/d (1.0 mmol/L) in men or < 50 mg/dL(1.3 mmol/L) in women, or receiving drug therapy for reduced HDL-C
    5) Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women
39. **NPO**: nil per os, nothing by mouth
40. **LAGB:** Laparoscopic Adjustable Gastric Band
41. **LDL:** Low-density lipoprotein
42. **NSAIDs:** Non-steroidal anti-inflammatory drugs
43. **Obesity Class:** moderate (Class I, BMI 30.0 – 34.9), severe (Class II, BMI 35.0 – 39.9), and very severe (Class III, BMI > 40)
44. **OTC:** Over the Counter
45. **PCP:** Primary care provider
46. **POWER-UP**: Practice-based Opportunities for Weight Reduction trial at the University of Pennsylvania
47. **% TBL:** Percent Total Body Weight Loss, calculated as:
    a. (Weight(kg)BL – Weight(kg)FUP)/Weight(kg)BL
    b. Where Weight(kg)BL is the subject's weight at baseline in kilograms and Weight(kg)FUP is the subject's weight at follow-up in kilograms.
48. **PHQ-9:** Patient Health Questionnaire 9
49. **PPIs:** Proton Pump Inhibitors
50. **PTFE**: Polytetrafluroroethylene
51. **RYGB**: Roux-en-Y Gastric Bypass
52. **SSC:** Study Steering Committee
53. **SADE**: Serious Adverse Device Effect
54. **SAE: Serious Adverse Event:** defined as an adverse event that
    a. led to a death
    b. led to a serious deterioration in health resulting in
        i. a life threatening illness or injury
        ii. a permanent impairment of a body structure or body function

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

c. led to fetal distress, fetal death or a congenital abnormality or birth defect

55. **SOS**: Swedish Obesity Study
56. **TOS**: The Obesity Society
57. **TPS**: TransPyloric Shuttle
58. **TPSS**: TransPyloric Shuttle System
59. **VBG**: Vertical Banded Gastroplasty
60. **UADE: unanticipated adverse device effect** are any serious adverse device effects on health, safety or any life-threatening problem or death caused by, or associated with the investigational study device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including IFU) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
61. **Ulcer:** defined as a defect in the gastric or duodenal wall ≥ 5mm in diameter with unequivocal depth.
62. **(Prolonged) vomiting**: more than 4-6 times in 24 hours
63. **(Recurrent) vomiting**: every day over 3-5 days
64. **Weight Stability:** a < 5% change in body weight for at least 3 months prior to the screening visit

APPENDIX B: SCHEDULE OF EVENTS

Evaluation	Visit	Screen	Baseline	Index Procedure	1wk	1M	2M	4M	6M	7M	8M	9M	10M	11M	12M
	Days	Within 56 days	Within 7 days	Day 0	D7 ±2	D30 ±7	D60 ±14	D120 ±14	D180 ±14	D210 ±7	D240 ±7	D270 ±21	D300 ±7	D330 -14	D365 ±30
Informed consent		X													
Patient demographics		X													
Medical history		X													
Current medication		X	X	X	X	X	X	X	X			X			X
Psychological evaluation		X													
Inclusion criteria		X	X												
Exclusion criteria (general)		X	X												
Exclusion criteria (endoscopic)				X											
Lifestyle counseling			X		X	X	X	X	X			X			X
Follow up telephone call										X	X		X	X	
Height		X													
Weight		X	X	X	X	X	X	X	X			X			X
BMI		X	X	X	X	X	X	X	X			X			X
Body circumference		X	X	X	X	X	X	X	X			X			X
Physical exam		X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]			X[1]			X
EKG		X													
CBC w/differential		X	X												
Chemistry panel 20		X	X												
Blood tests[2]		X	X						X						X
Urine pregnancy test		X	X												
Stool H pylori test		X													
Patient Health Questionnaire		X													
IWQOL-Lite			X						X						X
Satiety Assessments (VAS & Eating Inventory)			X		X	X			X						X
[redacted]		[redacted]													
Adverse event assessment				X	X	X	X	X	X			X			X
Blinding assessment					X										X
Device removal															X
Study exit															X

1 – Abbreviated physical: temperature, systolic/diastolic blood pressure, respiration rate, heart rate
2 -- Blood tests include lipid panel, fasting blood glucose, insulin, HbA1c, C - reactive protein
3 – For Treatment group only
[redacted]

APPENDIX C: LIFESTYLE MODIFICATIONS PROGRAM...REDACTED

APPENDIX D: BMI CALCULATOR

To calculate the subject's Body Mass Index, using the website below:

http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htmEnter the subjects Weight and Height and then calculate BMI (print screen for source documentation)

Formulas used to calculate Body Mass Index:

English BMI Formula

BMI = Weight in pounds/ (height in inches x height in inches) x 703

Metric BMI Formula

BMI = Weight in kilograms/ (height in meters x height in meters)

Note that BMI may also be calculated within the eCRF.

APPENDIX E: SAMPLE OF PATIENT HEALTH QUESTIONAIRE (PHQ-9)… REDACTED

APPENDIX F: IWQOL – LITE…REDACTED

APPENDIX G: SAMPLE OF SUBJECT INFORMATION CARD

<< Front of the Card>>

If you are required to see your doctor for other medical conditions, please show this card to your doctor.
PLEASE CARRY THIS CARD AT ALL TIMES

Patient Card for the ENDObesity® II Study

Model #: _____

Device Lot #: _____

Date of Implant: _____

Investigator Physician's contact information: _____ at (XXX) XXX-XXXX

*This person is participating in a **double-blind** weight loss study and may or may not have a TransPyloric Shuttle® in his/her stomach. The TransPyloric Shuttle may slow down the food and medication from passing through stomach. For questions regarding the TransPyloric Shuttle and the ENDObesity II Study, please contact the Investigator. *Please do not disclose to the subject any findings that may indicate randomization assignment without discussion with the Investigator.*

BARONova BAROnova, Inc., 1509 Industrial Road, San Carlos, CA 94070, USA, Telephone: (844) 870-6682

<< Back of the Card>>

MRI SAFETY INFORMATION

Non-clinical testing has demonstrated the BAROnova TransPyloric Shuttle® (TPS) is MR Conditional.
A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 3-Tesla or less
- Maximum spatial field gradient of 4,000 gauss/cm (40 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 4 W/kg (First Level Controlled Operating Mode)

APPENDIX H: SAMPLE OF CONTROL OF EATING QUESTIONAIRE…REDACTED

APPENDIX I: EATING INVENTORY…REDACTED