Safety and Efficacy of Endoscopically Placed Intragastric Balloon in Obese Adolescents with Comorbidities - A Pilot Study

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Study Product:	Orbera Intragastric Balloon (Apollo Endosurgery, Austin, TX)
Protocol Number: (IRBe)	15-009191
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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ASGE	American Society of Gastroenterology and Endoscopy
BIB	BioEnterics Intragastric Balloon
BMI	Body Mass Index
BP	Blood Pressure
CES-D	Self-Report Depression Scale Questionnaire
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DM2	Diabetes Mellitus Type 2
DSMB	Data and Safety Monitoring Board
EBT	Endoscopic Bariatric Therapy
EGD	Upper Endoscopy
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal/Gastroenterology
H. pylori	Helicobacter pylori
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
IDE	Investigational Device Exemption
IGB	Intragastric Balloon
IRB	Institutional Review Board
MCHS	Mayo Clinic Health System
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic Steatohepatitis
PE	Physical Exam
PHI	Protected Health Information
PI	Principal Investigator
PMA	Premarket Approval
PN Q	Pediatric Nutrition Questionnaire
SAE	Serious Adverse Event/Serious Adverse Experience
SCAS	Spence Child Anxiety Scale Questionnaire
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SOP	Standard Operating Procedure
TBWL	Total Body Weight Loss
UADE	Unanticipated Adverse Device Effect
US	Ultrasound
WMC	Weight Management Clinic

Study Summary

Title	Safety and Efficacy of Endoscopically Placed Intragastric Balloon in Obese Adolescents with Comorbidities – A Pilot Study
Running Title	IGB in Obese Adolescents with Comorbidities
IRB Protocol Number	15-009191
Phase	Pilot
Methodology	Open Label
Overall Study Duration	60-64 Weeks
Subject Participation Duration	12 months
Objectives	• Determine if placement of IGB for a period of 6 months is safe and results in weight loss with metabolic improvement in obese adolescents • Determine if IGB is well tolerated by adolescents • Determine if weight loss is sustainable after the IGB removal through integrating the subjects in the pediatric weight management program
Number of Subjects	12
Diagnosis and Main Inclusion Criteria	Subjects must have BMI>35 kg/m^2 with one severe comorbidity or BMI>40 kg/m^2 with two or more mild comorbidities
Study Device	Orbera Intragastric Balloon (Apollo Endosurgery Austin, TX)
Duration of Exposure	6 months
Statistical Methodology	The study results will be largely descriptive. Standard statistical analysis will be performed. Multiple linear and logistic regression analysis will be performed to determine significant variables relating to risk. A p-value of < 0.05 will be considered statistically significant.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations and Mayo Clinic policies and procedures.

1.1 Background

The global rise in the prevalence of overweight and obesity among all ages and ethnic groups has become an epidemic that affects daily medical practices everywhere. The prevalence of pediatric obesity in the United States defined by a body mass index (BMI) measurement of ≥ 95% or greater than 2 standard deviation (SD) age has increased from 4.2% 1965 to 17.6% now. This significant increase in pediatric obesity is becoming a major health problem in United States.[1-3] The contributory causes of this rapid increase are multifactorial including metabolic dysregulation, genes, environmental/socioeconomic stressors, and energy imbalance.[4] Pediatric obesity is known to be associated with increased morbidity and predisposes adolescents to become obese adult with long term complications. Obese children and adolescents are at increased risk for obstructive sleep apnea, metabolic syndrome, orthopedic disorders, hypertension, type 2 diabetes mellitus (DM2), and fatty infiltration into the liver that can range from nonalcoholic fatty liver disease (NAFLD) to nonalcoholic steatohepatitis (NASH) and cirrhosis. [5, 6] These comorbidities are also clearly associated with significant increase in outpatient visits, prescription drug use, and emergency room visits, resulting in decrease quality of life for these adolescents and significant increase medical care cost. [7] In view of the magnitude of the pediatric obesity problems, many centers are developing multidisciplinary approach programs to address childhood obesity and prevent its long-term complications. The current generalized approach usually includes changes in lifestyle, diet, and physical activity.[8] The challenge to this approach is that persistent lifestyle changes are difficult to achieve and long-term results are often disappointing.[9, 10] For all of these reasons, adolescents are increasingly undergoing surgical treatment for obesity, and systematic data collection in bariatric programs is needed to further shape adolescent bariatric surgery guidelines.[11] The paucity of long-term outcome and special ethical consideration created a major limitation to establishing unified indications and criteria for bariatric intervention in adolescents.[12] New research is underway with the intent to produce specific recommendations and guidelines for bariatric intervention in adolescents, based on numerous positive publications regarding the clinical impact of bariatric intervention on the early-onset obesity-related diseases.[13-16]

1.2 Investigational Device

The Orbera (Apollo Endosurgery, Austin, TX) is an elastic spherical balloon made of silicone, filled with 550 mL of saline solution, and is FDA approved for weight loss in adult US patients with body mass index between 30 to 40 kg/m^2. The deflated balloon comes preloaded on a catheter, which is blindly advanced trans-orally into the stomach. An endoscope is then advanced alongside it to ensure accurate placement of the balloon in the fundus. Under direct visualization, the balloon is then inflated by injecting saline solution through the external portion of the catheter. The Orbera balloon is currently used outside the United States including

a pilot trial for adolescent in the United Kingdom.[17] This intragastric balloon is typically implanted for 6 months and then retrieved endoscopically.

1.3 Preclinical Data

See PMA study of the Orbera intragastric balloon.

1.4 Clinical Data to Date

The Orbera™ Intragastric Balloon (Apollo Endosurgery, Austin, TX), previously known as the BioEnterics Intragastric Balloon (BIB) (Allergan, Irvine, CA) is an elastic spherical balloon made from silicone, filled with about 600 ml of saline and is placed in the stomach via upper endoscopy. This intragastric balloon (IGB) is designed to stay in place for 6 months prior to endoscopic removal and has been widely used in Europe, South America, and the Middle East with excellent safety profile. In an American Society of Gastroenterology and Endoscopy (ASGE) Bariatric Endoscopy Task Force systematic review and meta-analysis the pooled percentage of total body weight loss (TBWL) after the Orbera IGB implantation was 12.3% (95% CI, 7.91–16.73), 13.16% (95% CI, 12.37–13.95), and 11.27% (95% CI, 8.17–14.36) at 3, 6, and 12 months after implantation, respectively.[18] This was based on a review of 55 studies. This balloon is currently FDA approved for use in the United States after a US randomized multicenter pivotal trial demonstrated similar efficacy. There is paucity of data about the use of IGB in adolescents. Despite the preference for avoiding surgical and invasive intervention for managing morbid obesity in adolescents, high relapse rates of current approaches and minimal adverse events of IGB can justify this nonsurgical bariatric interventions.[19] A recent pilot study suggested that IGB was a feasible and safe intervention in obese adolescents resulting in weight loss and improvement in their metabolic syndrome. [17] Another important application to this intervention comes from the noticeable increase in the incidence NAFLD and NASH in adolescents is increasing, resulting in significant morbidity and long-term complications such as liver fibrosis and cirrhosis.[20] Neuman et al, suggested that bariatric procedures including noninvasive ones such as IGB intervention can resolve the liver involvement and prevent further complications.[21]

Another application comes from the growing evidence regarding the epidemiology of DM2 in adolescents and its multisystem health complications, but treatment options have lagged behind. Disease progression in adolescents occurs despite aggressive medical therapy and tends to be more aggressive than in adults with DM2. All of that evidence resulted in increased interest in the application of bariatric intervention for adolescents with DM2 and morbid obesity. This was the recommendation of recent review by Shah et al, who recommended bariatric intervention because of the evidence demonstrating improvement or remission in many adults with diabetes after bariatric intervention. [22]

The rates of adverse events after implantation of the Orbera balloon are pooled from a manual review of 68 studies (8500 implantations) and are summarized in Figure 1. Pain and nausea are frequent side-effects after Orbera balloon implantation, occurring in up to 33.7% of subjects. Medications such as proton pump inhibitors, antispasmodic drugs, and antiemetics are usually prescribed prophylactically before, during, and after balloon placement to prevent

or minimize these expected common side effects. Serious side-effects with Orbera balloon are rare with an incidence of migration and gastric perforation of 1.4% and 0.1%, respectively. Most of the reported perforations with the Orbera were in patients who had undergone previous gastric surgeries, which is a contraindication for use in the US.[18]

1.5 Study Rationale and Risk/Benefits

1.5.1 Study Rationale

Recent advances in the endoscopic bariatric therapies (EBTs) provided an alternative effective and minimally invasive treatment approach to obesity that would increase treatment options beyond surgery, medications, and lifestyle measures. Due to the special ethical consideration of involving minors in empirical therapies, the reversible EBTs might be more viable option for managing obesity in adolescents and prevent long-term complications. One of the EBT approaches is the intragastric balloon (IGB) which involves an endoscopic device for temporary nonpharmaceutical and nonsurgical treatment for morbid obesity.[23] The Orbera Intragastric Balloon (IGB) (Apollo Endo-surgery, Austin, TX) is an elastic spherical balloon made from silicone, filled with about 600 ml of saline and is placed in the stomach via upper endoscopy. The IGB is designed to stay in place for 6 months prior to endoscopic removal. The Orbera IGB was approved for use in adults in August of 2015. The IGB has been widely used in Europe, South America, and the Middle East with excellent safety profile. A recent review and metaanalysis by Abu Dayyeh et al, of 8506 IGB implantation showed that IGB resulted in significant weight loss (up to 15%) with serious adverse events rate of 0.3-0.1% mostly in patient with prior gastric surgery.[24] Recent trials in adolescents with obesity have confirmed the safety and feasibility of using the IGB as a weight management tool in adolescents with morbid obesity.[15, 16] As discussed above, IGB could also be useful in treating NAFLD, NASH and DM2 in adolescents.

1.5.2 Anticipated Risks

The rates of adverse events after implantation of the Orbera balloon are pooled from a manual review of 68 studies (8500 implantations) and are summarized in Figure 1. Pain and nausea are frequent side-effects after Orbera balloon implantation, occurring in up to 33.7% of subjects. Medications such as proton pump inhibitors, antispasmodic drugs, and antiemetics are usually prescribed prophylactically before, during, and after balloon placement to prevent or minimize these expected common side effects. Serious side-effects with Orbera balloon are rare with an incidence of migration and gastric perforation of 1.4% and 0.1%, respectively. Most of the reported perforations with the Orbera were in patients who had undergone previous gastric surgeries, which is a contraindication for use in the US.[18]

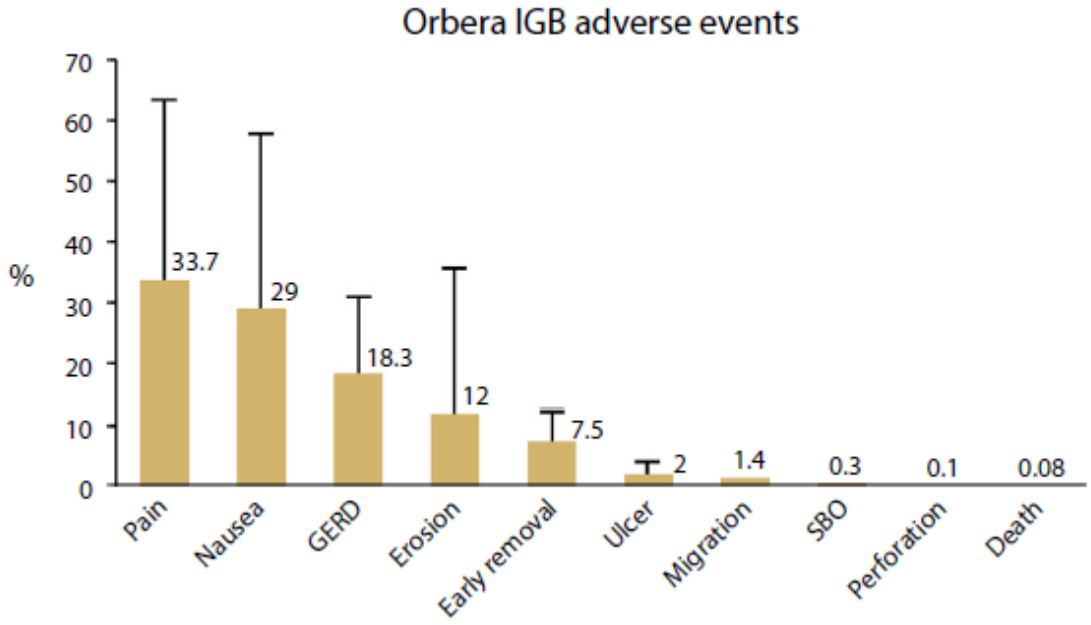

Figure 1. Pooled Orbera Complications from 68 studies (8500 patients) [24]

As with all endoscopic and/or implant procedures, serious injury or death can occur. With any device, there is always a chance of developing problems from the treatment. Not all risks or problems associated with the use of the Orbera Intragastric Balloon are known. Common risks that can occur include nausea, vomiting, abdominal pain, gastroesophageal reflux disease, and bad breath. This is expected due to the physical presence of the balloon in the subject's stomach. Anti-nausea medications may be given on the procedure day and should help with any nausea and vomiting that the subject may have. The side effects and risks of the medication the subject may be prescribed will be discussed with the subject by the study PI (Dr. Absah) prior to the balloon procedure.

Per the Orbera Directions For Use (revision 2), possible complications from the use of ORBERA IGB include:

- Intestinal obstruction by the balloon which could require surgery or endoscopic removal of the balloon
- Death due to complications related to intestinal obstruction
- Esophageal obstruction which could require surgery or endoscopic removal of the balloon
- Gastric outlet obstruction which could require surgical removal of the balloon
- Injury to the digestive tract during placement of the balloon in an improper location which could cause bleeding and perforation and in turn could require surgical correction
- Insufficient or no weight loss
- Adverse health consequences resulting from weight loss
- Gastric discomfort, feelings of nausea and vomiting following balloon placement

- Continuing nausea and vomiting or possibly the prevention of vomiting
- A feeling of heaviness in the abdomen
- Abdominal or back pain, either steady or cyclic
- Gastroesophageal reflux
- Influence on digestion of food
- Blockage of food entering into the stomach
- Bacterial growth in the fluid which fills the balloon which could cause infection, fever, cramps, and diarrhea
- Injury to the lining of the digestive tract as a result of direct contact with the balloon, grasping forceps, or as a result of increased acid production by the stomach which could lead to ulcer formation and possible surgical correction
- Death due to complications related to gastric or esophageal perforation
- Balloon deflation and subsequent replacement
- Acute pancreatitis
- Spontaneous over inflation

Possible risks which may occur from the subject's endoscopy procedure include difficulty swallowing, injury to the lining of the esophagus or stomach, perforation (a hole in the wall of your stomach or esophagus), bleeding, infection, inflammation, dental injury, pain following the procedure with the potential for hospitalization to control pain, post procedure fluid collection with or without abscess or death.

The risk of monitored controlled sedations medications used to make the subject drowsy can cause breathing difficulties or a drop in blood pressure. These side effects are easily observed and managed by the anaesthesia team. These medications may cause some inflammation at the intravenous site where the drugs are given again that will be discussed and explained by the anaesthesia team prior to the procedure.

If any gastric ulceration were identified at the time IGB removal after 6 months, subjects will be treated with proton pump inhibitors therapy with dose and duration of therapy determined by the study PI. These subjects will be followed clinically until complete resolution.

1.5.3 Potential Benefits

The Orbera intragastric balloon is expected to result in 12.3%, 13.16 and 11.27% total body weight loss (TBWL) at 3, 6, and 12 months after implantation, respectively, based on recent review.[18] This balloon is currently FDA approved for use in adults in the United States. Other potential benefits include improving the metabolic syndrome manifestation such as:

1. Sustainable decrease in baseline heart rate (>10 beats/min) and systolic blood pressure (>10 mmg/hg)
2. Normalization of liver function panel
3. Decrease in fatty liver infiltration on liver ultrasound (US)
4. Decrease in Hg1Ac level

5. Improvement of fasting lipid profile
6. Increase in activity level

2 Study Objectives

Primary Objective:

Assess the safety and effectiveness of an intragastric balloon device in obese adolescent subjects with comorbidities to assist with weight reduction and reverse metabolic complications.

The intended use for the subject device (IGB) in adolescents is to induce > 10% total body weight loss in morbidly obese adolescents.

Specific Aims:

- Determine if placement of IGB for a period of 6 months is safe and results in weight loss and metabolic improvement in obese adolescents
- Determine if intragastric balloon is well tolerated by adolescents
- Determine if weight loss is sustainable after the IGB removal through integrating the subjects in the pediatric weight management program

Study Protocol Hypothesis:

Intragastric balloon is a safe, well tolerated and effective intervention for weight loss and decreasing obesity complications in adolescents with comorbidities.

3 Study Design

3.1 General Design

Potential subjects will be seen by a pediatric endocrinologist (Dr. Kumar) or a pediatric gastroenterologist (Dr. Absah) who will review and approve the potential subject's inclusion and exclusion criteria. For interested subjects who have met all the inclusion and exclusion criteria, assent will be obtained from the subject and consent will be obtained from the parent/legal guardian. After consent, the subject will be given three questionnaires to complete at home and return at the baseline visit; the PN Q will be returned to and reviewed by the dietitian in the weight management clinic (WMC), and the CES-D and SCAS will be returned to and reviewed by the psychologist.

At baseline, subjects will be seen by the pediatric weight management multidisciplinary team consisting of a pediatric endocrinologist (Dr. Kumar) or a pediatric gastroenterologist (Dr. Absah) for a physical examination; a registered dietitian in the WMC; and a psychologist. Blood, urine, and stool samples will be collected at baseline. Food record templates will be provided to study subjects to be completed for three days prior to each future WMC visit.

The baseline requirements may all be completed in one day, or they may be completed on separate days depending on scheduling times and the subject's availability. Female subjects will also have a urine pregnancy test in the morning before the procedure.

If the subject still meets all the inclusion and exclusion criteria after the baseline evaluations and the pregnancy test are completed, s/he will undergo physical examination followed by placement of the IGB by a gastroenterologist (Dr. Absah or Dr. Abu Dayyeh) via endoscopic approach under monitored and controlled anesthesia. Esophagogastroduodenoscopy (EGD) is very safe and routine diagnostic approach for adolescents with gastrointestinal disorders.[25] The balloon will remain in the stomach if tolerated for 6 months, and then it will be removed endoscopically by a gastroenterologist (Dr. Absah or Dr. Abu Dayyeh). In order to prepare for the IGB removal, the subject will need to be on a liquid diet for 48 hours prior to its removal, and consume nothing by mouth for at least 12 hours prior to the IGB removal. Subjects will be informed that the risk for complications increases after 6 months and that it is imperative that the balloon is removed at 6 months, otherwise the subject assumes the additional risks.

The multidisciplinary team consisting of a pediatric endocrinologist or pediatric gastroenterologist, and a dietitian at the weight management clinic, will evaluate the patient at baseline, at 3 and 6 months after the insertion of the balloon, and at 9 and 12 months, which would be after the removal of the balloon. The dietitian at the weight management clinic will review the PN Q and the food record template and guide the diet modification accordingly. Subjects will have follow up psychology visits to support adherence and address any emotional and social adjustment concerns. Blood and urine samples will also be collected at months 3, 6, 9 and 12, after the IGB insertion. The subjects and their parents will be contacted by phone by a GI nurse to answer telephone questionnaire in between the visits on site at 4 days, 2 weeks, and at months 1, 2, 4, 5, 7, 8, 10, and 11, after the IGB insertion.

Blood Samples: Eight to twelve hour fasting blood samples will be collected at baseline, 3, 6, 9, and 12 month visits including:

- CBC with differential
- Electrolytes panel (Sodium, Potassium, Calcium, Creatinine, Chloride, Bicarbonate, BUN)
- Liver function tests (AST, ALT, Alkaline phosphatase, Total Bilirubin, Total Protein, Albumin)
- Nutritional assessment (Fe/TIBC, B12, Folic Acid, 25-Hydroxy Vitamin D, Ferritin)
- Coagulation panel (ProTime/INR, PTT)
- Total Cholesterol/Lipid panel
- Thyroid function tests, PTH
- Insulin
- Glucose
- CRP
- HgA1c

The effect of the IGB on the GI physiology will be assessed by collecting the following GI hormones at baseline and at 3, 6, 9 and 12 months: Total Ghrelin; PYY; GLP-1; and Leptin.

In total, approximately 40 ml of blood will be drawn for all blood tests.

Urine Sample: A urine sample will be collected at baseline, 3, 6, 9, and 12 months.

Stool Sample: A stool sample will be collected for a fecal antigen study for Helicobacter pylori (H. pylori) (sensitivity > 96.8%) to exclude the presence of H. pylori prior to the initial endoscopic assessment.

3.2 Primary Study Endpoints

The primary endpoint will be achieving ≥ 10% total body weight loss (TBWL).

3.3 Secondary Study Endpoints

The secondary endpoints will be:

1. Evaluating the effect of the weight loss on the adolescents' overall health and mental health using the well-being questionnaires, CES-D and SCAS, prior to IGB insertion, while the IGB is in place, and after the IGB removal.
2. Assessing the effect of weight loss on obesity side effects by monitoring changes in liver enzymes, fasting insulin, HgA1c, and lipid profile.

3.4 Primary Safety Endpoints

- Incidence of all serious adverse events including unanticipated adverse effects (balloon migration, small bowel obstruction, luminal GI perforation, ulcer formation, liver abscess formation, bleeding, biliary obstruction or injury, aspiration, infection, abdominal pain requiring hospitalization, nausea and dehydration requiring intravenous fluids, and death). All adverse events will be captured and graded for severity using Common Terminology Criteria for Adverse Events (CTCAE) scale. [27]
- Early balloon intolerance requiring removal.

- Balloon deflation rates (see Orbera PMA)

4 Subject Selection, Enrollment and Withdrawal

Adolescents age 14-17 who are seen at Mayo Clinic-Rochester in community pediatrics, pediatric GI, pediatric endocrinology, or the pediatric weight management clinic, or at Mayo Clinic Health System (MCHS) with a BMI>35 kg/m^2 with one severe comorbidity or BMI>40 kg/m^2 with two or more mild comorbidities as per the ESPAGHAN guidelines for

bariatric intervention in children with severe obesity. [14] Recent meta-analysis supported the safety and benefit of IGB use in higher BMI (range 35-55).[24] Subjects that meet these criteria can be referred to the PI, co-investigators, or study coordinator to approach for possible participation in this research study.

4.1 Inclusion Criteria

This study will aim to recruit adolescents age 14-17 years with the BMI criteria and the comorbidities summarized in Table 1.

Table 1: Primary inclusion criteria for bariatric intervention in adolescents:

BMI>35 kg/m^2 with **one** of the following **severe comorbidities, both for at least 2 years**:

1. Type 2 diabetes mellitus
2. Moderate-to-severe sleep apnea
3. Pseudotumor cerebri
4. NASH based on fatty infiltration of the liver with transaminitis that cannot be explained by other liver disease

Or

BMI>40 kg/m^2 with **two or more** of the following **mild comorbidities, all for at least 2 years**:

1. Hypertension
2. Dyslipidemia
3. Mild obstructive sleep apnea
4. Chronic venous insufficiency
5. Panniculitis
6. Urinary incontinence
7. NASH
8. Gastroesophageal reflux disease
9. Arthropathies related to weight

Table 1 modified from [14].

In addition, **all** of the following inclusion criteria must be met. The subject must have:

1. attained approximately 95% of adult stature, as demonstrated by Tanner Stage IV or more and growth charts demonstrating the taper/plateau of height as a marker for achieving 95% of the subject's adult stature. Height will be measured by trained staff to the nearest 0.1 cm using a stadiometer attached to a wall and documented in the subject's EMR. In the absence of previous growth charts, skeletal maturity will be documented by a bone age of at least 13 years in girls and 15 years in boys; and
2. failed to attain a healthy weight with at least one experience with medically supervised lifestyle changes, including physical activity and dietary interventions, which will be clearly documented in the subject's medical record, and

3. demonstrated commitment to psychological evaluation perioperatively, in which the pediatric psychologist with expertise in childhood obesity must confirm that the subject has the maturity and stable psychosocial environment necessary for this research study and has validated the CES-D and SCAS surveys completed by the subject, and
4. agreed to avoid pregnancy for 1 year after IGB placement through abstinence or approved contraception as noted in Appendix A (female subjects only), and
5. agreed to adhere to nutritional guidelines after IGB placement, as provided by weight management clinic dietitian, and
6. decisional capacity and desire to provide informed assent in conjunction with parent/guardian consent, and willingness to comply with all study requirements, and
7. hypertension stage I: systolic blood pressure and/or diastolic blood pressure ≥ 95th percentile, OR high normal blood pressure between the 90th and 95th percentile.

   Note: Patients with hypothyroidism that is treated and are persist to have morbid obesity despite adequate thyroid replacement therapy can be recruited.

4.2 Exclusion Criteria

Subjects will be excluded if:

1. they are pregnant or breastfeeding, or
2. there is any other disease, physical examination finding, or clinical laboratory result that provides a reasonable suspicion of a disease or condition that contraindicates the use of the investigational device or that may affect the interpretation of the results or render the subject at high risk for treatment complications, or
3. there is alcohol, tobacco, or substance use by the subject, or
4. in the opinion of the PI and/or co-investigators, subject or parent/guardian may be non-compliant with study schedules or procedures, or
5. there are any endoscopic contraindications, including large hiatal hernia (≥ 2 cm), esophagitis of any degree, erosive gastritis, or ulceration of the stomach or duodenum, or
6. H. pylori is detected via a fecal antigen study prior to initial endoscopic assessment (sensitivity > 96.8%); once treated, a repeat fecal antigen must be performed to document eradication prior to the first endoscopic approach for balloon placement, or
7. they have hypertension stage II > 99th percentile, unless they had a complete workup to exclude secondary etiologies other than being overweight, or
8. Gastroesophageal reflux disease (GERD) subjects are on more than one medication or have a history of erosive esophagitis due to GERD, or
9. they have dyslipidemia, if part of hereditary metabolic syndrome or genetic disorder, or
10. they have any gastrointestinal disease that can result in stomach ulcerations, such as Crohn's disease, celiac disease, eosinophilic esophagitis, acute or chronic pancreatitis or gastrinoma, or
11. they have any endocrine disorders that affect metabolic status of the subjects, such as untreated hypo/hyperthyroidism, type 1 diabetes, Cushing's disease, or adrenal

insufficiency, as documented in the EMR through an evaluation by the pediatric endocrinologist who will order additional testing if needed, or

12. they have prior gastrointestinal surgery with sequelae, i.e. obstruction, and/or adhesive peritonitis or known abdominal adhesions and/or history of abdominal and/or pelvic surgery which may cause adhesions (except one of the following: caesarean section, diagnostic laparoscopy, laparoscopic appendectomy, laparoscopic cholecystectomy performed 12 or more months prior to balloon implantation), or
13. they have prior open or laparoscopic bariatric surgery, or
14. they have prior surgery of any kind on the esophagus, stomach or any type of hiatal hernia surgery, or
15. they have any inflammatory disease of the gastrointestinal tract including esophagitis, Barrett's esophagus, cancer or specific inflammation such as Crohn's disease, or
16. they have potential upper gastrointestinal bleeding conditions such as esophageal or gastric varices, congenital or acquired intestinal telangiectasis, or other congenital anomalies of the gastrointestinal tract such as atresias or stenoses, or,
17. they have a gastric mass, or
18. they have acid reflux symptoms to any degree that require more than one medication for symptom control, or
19. they have a structural abnormality in the esophagus or pharynx such as a stricture or diverticulum that could impede passage of the balloon alongside the endoscope, or
20. they have achalasia or any other severe esophageal motility disorder that may pose a safety risk during the removal of the device, or
21. they have severe coagulopathy, or
22. they have poorly controlled diabetes, defined as having a HgA1c > 10, or
23. they have serious health conditions unrelated to their weight that would increase the risk of endoscopy, or
24. they have chronic abdominal pain, or
25. they have motility disorders of the GI tract such as gross esophageal motility disorders, gastroparesis, or intractable constipation, or
26. they have hepatic insufficiency or cirrhosis, or
27. they have serious or uncontrolled psychiatric illness or disorder that could compromise their understanding of, or compliance with, follow-up visits and removal of the device, or
28. they are receiving daily prescribed treatment with aspirin, anti-inflammatory agents, anticoagulants or other gastric irritants, or
29. they are taking medications on specified hourly intervals that may be affected by changes to gastric emptying, such as anti-seizure or anti-arrhythmic medications, or
30. they are taking corticosteroids, immunosuppressants, or narcotics, or
31. they are unable or unwilling to take prescribed proton pump inhibitor medication, or
32. they are known to have, or suspected to have, an allergic reaction to materials contained in the system, or
33. they have ever developed a serotonin syndrome and are currently taking any drug known to affect the levels of serotonin in the body (e.g. selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors), or

34. they have a medically identifiable cause of obesity (specific diagnosed genetic or hormonal case for obesity such as hypothyroidism or Prader Willi syndrome), or
35. they have known history of endocrine disorders affecting weight, or
36. they use any medications, except for Metformin, known to affect body weight and carbohydrate or lipid metabolism, or
37. they used an intragastric device prior to this study, or
38. they participated in any clinical study which could affect weight loss within the past 6 months, or
39. they have symptomatic congestive heart failure or cardiac arrhythmia, or
40. they have a diagnosis of an autoimmune connective tissue disorder (e.g. lupus, erythematous, scleroderma), or immunocompromised, or
41. they are on insulin for type 2 diabetes and not proficient in self-monitoring capillary blood glucose testing.

4.3 Subject Recruitment, Enrollment and Screening

IRB approved fliers will be distributed to physicians in the following areas, informing them about this study and the primary inclusion criteria: Mayo Clinic-Rochester community pediatrics, pediatric GI, pediatric endocrinology, and the pediatric weight management clinic; and Mayo Clinic Health System (MCHS). The primary inclusion criteria listed will be a BMI>35 kg/m2 and one severe comorbidity or BMI>40 kg/m2 with two or more mild comorbidities. Adolescents age 14-17 who meet these primary inclusion criteria can be referred to the PI, co-investigators, or study coordinator to approach for possible participation in this research study.

Potential subjects will be seen by a pediatric gastroenterologist (Dr. Absah) or pediatric endocrinologist (Dr. Kumar) who will review and approve the potential subject's inclusion and exclusion criteria. For interested subjects who have met all the inclusion and exclusion criteria, a study team member will review the risks, benefits, and alternatives with the subject and his/her parent/guardian. Sufficient time will be given to the subject and his/her parent/guardian to have all questions addressed by the study team and reflect on the decision to participate. If the subject and his/her parent/guardian are freely willing to proceed, a study team member will obtain assent from the subject and consent from the parent/legal guardian. After consent, the subject will be given three questionnaires to complete at home and return at the baseline visit; the PN Q will be returned to and reviewed by the dietitian in the weight management clinic, and the CES-D and SCAS will be returned to and reviewed by the psychologist.

At baseline, subjects will be seen by the pediatric weight management multidisciplinary team consisting of a pediatric gastroenterologist (Dr. Absah) or a pediatric endocrinologist (Dr. Kumar) for a physical examination; a registered dietitian in the weight management clinic; and a psychologist. Blood, urine, and stool samples will also be collected at baseline. The baseline requirements may all be completed in one day, or they may be completed on separate days depending on scheduling times and the subject's availability. Female subjects will also have a urine pregnancy test in the morning before the procedure.

If the subject still meets all the inclusion and exclusion criteria after the baseline evaluations and the pregnancy test are completed, s/he will undergo an endoscopic placement of the IGB balloon by a gastroenterologist and proceed with the remainder of the study as outlined in Section 6.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subject will be withdrawn from the study:

- Subject safety issues, adverse device effects
- Failure of subject to adhere to protocol requirements
- Subject decision to withdraw from the study (withdrawal of consent)

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a patient is withdrawn from the study for reasons other than severe adverse events, the IGB will be removed from the patient at a time that works for the patient and within 6 months of insertion. The patient will be followed as per the standard clinical protocol for the IGB to ensure safety. Weight and safety data will be collected until the IGB is removed. After IGB removal subjected will be followed clinically as per our protocol for additional six months to ensure safety.

5 Study Device

5.1 Description

The Orbera (Apollo Endosurgery, Austin, TX) is an elastic spherical balloon made of silicone, filled with 550 mL of saline solution, and is FDA approved for weight loss in adult US patients with body mass index between 30 to 40 kg/m^2. The deflated balloon comes preloaded on a catheter, which is blindly advanced trans-orally into the stomach. An endoscope is then advanced alongside it to ensure accurate placement of the balloon in the fundus. Under direct visualization, the balloon is then inflated by injecting saline solution through the external portion of the catheter. The Orbera balloon is currently used in many countries outside the United States and is typically implanted for 6 months and then retrieved endoscopically.

5.2 Method for Assigning Subjects to Treatment Groups

All enrolled subjects will get the Orbera intragastric balloon.

5.3 Preparation and Administration/Implantation of Investigational Device

The intragastric balloon will be used as described by the Orbera PMA application approved by the FDA, in adolescents who meet this protocol eligibility criteria described in Sections 4.1 and 4.2. See Section 5.1 for description of implantation.

Dr. Abu Dayyeh, Co-PI, has performed multiple studies with the Orbera balloon placement and was part of the pivotal trial. He will be physically supervising the endoscopic placement for all study subjects. Dr. Absah, PI, has 7 years of clinical experience (3 years of fellowship training and 4 years as a staff pediatric gastroenterologist), including performing endoscopic procedures. He will be receiving required course training through the manufacturing company upon approval of the study.

5.4 Subject Compliance Monitoring

The Orbera IGB will be advanced to the stomach under endoscopy guidance and inflated with approximately 600 ml of normal saline. Subject transient nausea and pain symptoms will be managed with few days course of antiemetic and antispasmodics as per our clinical practice. Subject and their parents will then receive a phone call by a GI nurse at 4 days after the procedure (± 1 day), then 2 weeks (± 1 week), at 1 month (± 1 week), and monthly thereafter (± 1 week) when not being seen for a physical exam and in the weight management clinic at months 3, 6, 9, and 12 (± 1 week), per the clinical protocol visit schedule for the IGB as indicated on Table 2. The PI will evaluate all subjects if the GI nurse feels they need to be evaluated based on results of telephone questionnaire.

At 6 months (± 1 week), the subject will return for balloon removal at the pediatric endoscopy unit under monitored pediatric anesthesia care. During this visit, the subject will have blood samples drawn; a physical exam by pediatric gastroenterologist (Dr. Absah) or pediatric endocrinologist (Dr. Kumar), followed by a meeting in the weight management clinic with the dietitian. Following the blood samples, PE, and WMC, the balloon will be removed at the same visit using the standard balloon retrieval kit approved by the FDA.

After balloon removal, all subjects will continue to be followed by the weight management team as indicated on Table 2. Weight, height, waist circumference, and demographic information will be collected at baseline, 3 months (± 1 week), time of balloon removal (6 months ± 1 week), 9 months (± 1 week), and at 12 months (± 1 week).

5.5 Prior and Concomitant Therapy

Prior and concomitant therapies include following the current weight management protocol which promotes diet and lifestyle changes to aid in weight reduction. Subjects' prior failed trial or coached programs for weight loss will be recorded in their medical records.

The multidisciplinary team consisting of a pediatric endocrinologist or pediatric gastroenterologist, and a dietitian at the weight management clinic, will evaluate the patient at baseline, at 3 and 6 months after the insertion of the balloon, and at 9 and 12 months, which would be after the removal of the balloon. The dietitian at the weight management clinic will review the PN Q and the food record template and guide the diet modification accordingly. Subjects will have follow up psychology visits to support adherence and address any emotional

and social adjustment concerns. Blood and urine samples will also be collected at months 3, 6, 9, and 12, after the IGB insertion. The subjects and their parents will be contacted by phone by a GI nurse to answer telephone questionnaire in between the visits on site at 4 days, 2 weeks, and at months 1, 2, 4, 5, 7, 8, 10, and 11, after the IGB insertion. Details of the diet and lifestyle regimen before and after the balloon insertion will be documented in the subject's medical records.

Before the balloon insertion, the number of calories recommended will be individualized based on the subject's age, gender, and level of physical activity, with a goal of achieving weight loss of 0.5 lb. per week. After the balloon insertion, the number of calories recommended will depend on the subject's current intake and weight trajectory. With regards to physical activity, subjects will be encouraged to engage in at least a total of 60 minutes of moderate to vigorous intensity physical activity on a daily basis.

For subjects with type 2 diabetes, the pediatric endocrinologist (Dr. Kumar) will be managing treatment for this co-morbidity while on the study. All medications that subjects are using during the study will be recorded at the start of the study and updated throughout the study on a medication reconciliation sheet. Subjects will be instructed to do self-monitoring of blood glucose, and the dose of medications for diabetes will be modified by pediatric endocrinology in order to prevent hypoglycemia or prevent worsening of diabetes. HgA1c will be measured every 3 months, and subjects will be reassessed for their diabetic condition every three months.

5.6 Packaging and Labeling

Upon receipt of the IGB devices from Apollo Endosurgery, assurance of the investigational device label will be affixed by the study coordinator to the packaging of each device. See below:

"CAUTION – Investigational Device. Limited by Federal (or United States) law to investigational use"

5.7 Masking/Blinding of Study

Not applicable

5.8 Receiving, Storage, Distribution and Return

5.8.1 Receipt of Investigational Devices

The Orbera IGB devices will be shipped to the study coordinator from Apollo Endosurgery in Austin, Texas. Upon receipt of the devices, the study coordinator will perform an inventory and fill out a device accountability log to ensure that all devices are accounted for. Any discrepancies, damaged, or unusable devices in a given shipment will be documented in the study files and the company will be notified. The devices will then be taken by the study coordinator to where they will be stored in the study coordinator's locked office space.

5.8.2 Storage

The Orbera IGB will be stored with the rest of the supplies that will be stored in the study coordinator's locked office space which is a secure location with limited access to prevent unintended or unauthorized use of the device.

5.8.3 Distribution of Study Device

The Orbera IGB will be distributed according to the clinical protocol of how clinical intragastric balloons are distributed. The serial number on the Orbera IGB will be matched up to a subject's medical record number. This de-identified data will then be recorded on the device accountability log using subject number instead of medical record number.

5.8.4 Return or Destruction of Study Device

At routine intervals and at the completion of the study, there will be a reconciliation of devices shipped, devices utilized, and devices remaining. This reconciliation will be logged on the Device Accountability form, signed and dated. Any discrepancies noted will be documented, the sponsor-investigator will be notified and an investigation will be conducted to determine the cause of the discrepancy. Devices destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Insertion of Balloon by PI or Co-PI

If the subject still meets all the inclusion and exclusion criteria after the baseline evaluations and the pregnancy test are completed, s/he will undergo physical examination followed by placement of the IGB by a gastroenterologist (Dr. Absah or Dr. Abu Dayyeh) via endoscopic approach under monitored and controlled anesthesia. Esophagogastroduodenoscopy (EGD) is very safe and routine diagnostic approach for adolescents with gastrointestinal disorders.[25]

6.2 Management of Symptoms after IGB insertion

Nausea management protocol will include the following:

- During the procedure, all subjects will receive a dose of dexamethasone, 4 mg intravenous, and one dose of ondansetron, 4 mg intravenous.
- After the procedure, subjects will be given ondansetron, 4 mg, every 4-6 hours, as needed. Phenergan, 12.5 mg twice a day, will be added as a rescue therapy.

Heartburn management protocol will include the following:

- All subjects will be started on omeprazole, 1 mg/kg, orally once daily or divided into 2 doses with a maximum of 20-40 mg per day for the entire duration the balloon is implanted.
- For continued symptoms despite omeprazole, an over-the-counter medicine such as Tums will be recommended.

For bloating, abdominal pressure or pain, if needed:

- Hyoscyamine sulfate immediate release sublingual, 0.125 to 0.25 mg orally every 4 hours or as needed will be given, with a maximum of 1.5 mg/day, as needed.

For diarrhea, if needed:

- Over-the-counter soluble fiber supplement such as psyllium 10 grams/day for two weeks will be suggested.
- If there is no response, stool pathogen studies will be considered to exclude any infectious etiologies.

For constipation which could develop during the liquid protein shake transitional diet, if needed:

- MiraLAX (polyethylene glycol), 17 grams in 8 oz of liquid daily, will be suggested.
- Continued use will be assessed during the following study visit or phone call.

If the subject continues to have symptoms for 1-2 weeks despite the aforementioned recommended medical treatment, the subject will be assessed clinically for overeating and dietary indiscretion which is the most common cause for continued symptoms in the intragastric balloon. If symptoms continue despite the recommended medical treatment and following the appropriate balloon diet, an abdominal ultrasound will be done to make sure that the balloon is still intact and in place. If symptoms persist and the balloon is still intact and in place, then the balloon will be removed due to intolerance.

For subjects with diabetes:

- Subjects will also receive a dose of dexamethasone, 4 mg intravenous.
- All subjects with type 2 diabetes will be on metformin or insulin prior to the balloon placement. The metformin would be discontinued 48 hours before the balloon placement and resumed after discharge from the hospital once oral intake has normalized. The metformin or insulin will be continued as needed and will be weaned only as tolerated based on blood glucose values and/or HgA1C, as determined by pediatric endocrinology.
- Subjects will be observed and undergo monitoring of their blood glucose values, and these children will be evaluated and closely followed by pediatric endocrinology in the perioperative period. All subjects will undergo a preanesthetic medical examination by a pediatric endocrinologist.
- Blood glucose values in these subjects would be measured prior to the procedure and subsequently every 4 hours during and for 48 hours after the procedure. Insulin

doses will be adjusted if there is an increase in blood glucose after dexamethasone administration. Insulin doses would also be adjusted by pediatric endocrinology in those subjects who are not able to tolerate oral intake or have hypoglycemia/hyperglycemia.

- Metformin, the only oral hypoglycemia approved for treatment of type 2 diabetes in children, would be discontinued prior to balloon placement in subjects on metformin monotherapy due to the risk of lactic acidosis. Blood glucose values would be monitored in the perioperative period. Subjects would receive insulin in the perioperative period in the event of hyperglycemia. Subjects on insulin, subjects who were on metformin prior to balloon placement, and subjects with any symptoms of hypoglycemia will be asked to monitor blood glucose in the post-operative period by performing self-monitoring of capillary blood glucose a minimum of 5 times daily (before each meal, at bedtime, and at 3 a.m.). Hyperglycemia will be managed by pediatric endocrinology. Metformin would be restarted after oral intake has normalized.
- All subjects will have a diabetes action plan in the medical records, at school, and at home that will clearly outline treatment for hypoglycemia.
- The balloon will be removed immediately if pediatric endocrinologist feels that medical management of hypo/hyperglycemia is challenging and/or has deteriorated by symptoms resulting from the insertion of the IGB.

6.3 Indications for Follow-up Endoscopy

After the balloon is inserted, an endoscopy will be required if:

- persistent abdominal pain
- GERD symptoms
- evidence of GI bleeding
- evidence of new microcytic anemia
- balloon deflation on abdominal ultrasound or x-ray

6.4 Indications for Removal of IGB

The balloon will be retrieved at the time of the endoscopy if the subject has any of the following:

- Esophagitis - Los Angeles grade C or D
- gastric or duodenal ulcers with high risk stigmata (visible vessel or sign of recent bleeding such as clots in the stomach) or deep ulcer that is more than 10 mm wide and 5 mm deep, worrisome for impeding perforation (see section below - Ulcers)
- balloon wedged in the antrum with clinical symptoms of gastric outlet obstruction or balloon partially/completely deflated

- new acute pancreatitis diagnosed by cross sectional imaging or serum lipase more than 3 times the upper normal limit for the institution (see section below - Pancreatitis)

Ulcers:

An ulcer will be defined as ≥ 5 mm in diameter with unequivocal depth by endoscopy. The ulcer is endoscopically significant if it is ≥ 3 cm in length and ≥ 1 cm in width. Effort will be made to capture clear images with an accessory of known dimensions next to the lesion to estimate size.

- If an ulcer is ≥ 2 cm in diameter or width (the smaller measurement between the length and width), or if there are any stigmata of increased risk of bleeding, such as visible vessels, clots, etc., the device will be removed.
- If an ulcer is smaller than 2 cm in diameter but endoscopically significant, signs of healing defined by a 25% reduction in either length or width should be observed after the first 8 weeks of medical therapy and a 50% reduction from baseline in either length or width after an additional 8 weeks of medication. If an endoscopically significant ulcer does not show signs of healing after 8 weeks of medication, shows less than 50% reduction in length or width after 16 weeks of medication, the device will be removed.
- Blood hemoglobin will be monitored during scheduled or unscheduled endoscopies in subjects who have ulcers or report signs of upper GI bleeding (hematemesis or melena).
- Subjects in whom an ulcer is diagnosed and treated will have endoscopic confirmation of complete resolution.

Pancreatitis:

New onset abdominal pain (developed after acute accommodative balloon symptoms of balloon placement has resolved) suggestive of pancreatitis (epigastric / right upper quadrant in location with or without radiation to the back, persistent (>3 hours in duration), and associated with nausea, vomiting, or new poor oral tolerance justify checking amylase and lipase levels.

- If pancreas enzymes are > 3X upper limit of normal for institution,
    - In a systemically ill patient with evidence of severe acute pancreatitis (requiring > 3 days hospitalization, OR evidence of end organ damage [acute renal failure, respiratory distress, or meeting SIRS (systemic inflammatory response syndrome) criteria for sepsis], OR cross sectional imaging suggestive of severe acute pancreatitis [evidence of pancreas necrosis or new pseudocyst], the balloon will be removed and close clinical follow-up of these severely ill patients will be required.
    - In a patient who does not meet the criteria of severe pancreatitis, pancreas enzymes will be repeated in 48 hours with clinical follow-up.
- If pancreas enzymes are < 3X upper limit of normal for institution,
    - In a systemically ill patient with evidence of severe acute pancreatitis (requiring > 3 days hospitalization, OR evidence of end organ damage [acute

renal failure, respiratory distress, or meeting SIRS (systemic inflammatory response syndrome) criteria for sepsis], OR cross sectional imaging suggestive of severe acute pancreatitis [evidence of pancreas necrosis or new pseudocyst], the balloon will be removed and close clinical follow-up of these severely ill patients will be required.
  - If typical pain persists for > 48-72 hours, pancreas enzymes will be repeated in 48 hours with clinical follow-up.
  - If pain resolves within 48-72 hours, clinical follow-up will be required.

In addition to the above mentioned endoscopic findings, the balloon would be removed in case of:

- severe anticipated or unanticipated adverse events
- pregnancy
- subject and family request for balloon removal
- risk of continuation of the trial, in the opinion of the PI, due to psychosocial circumstances, noncompliance with the required follow-ups and removal, or if the subject is moving and there is a risk of not being able to remove the balloon at 6 months.

Otherwise, the balloon will stay in place and the subject will be treated symptomatically, as described in Section 6.2.

6.5 Indications for Repeat Endoscopy after Removal of IGB

At the time of balloon removal, a repeat endoscopy will be indicated if the following conditions were found:

- Esophagitis - Los Angeles grade C or D
- Significant gastric ulceration (ulcers are bigger than 10 mm with high risk stigmata such as visible vessel, adherent clot, or clean base with > 5 mm depth)

If the gastric ulcers persist despite the proton pump inhibitor increase, then other etiologies will be excluded (Crohn's disease, celiac disease or hypergastrinemia) by performing mucosal biopsies from the ulcer and further blood work.

Subjects with any device related adverse events (AE) or gastric ulcerations at the time of device removal will continue on medical proton pump inhibitors therapy with dose and duration of therapy determined by the study PI. These subjects will be followed clinically until complete resolution. Repeat endoscopy to assess for resolution will be done at the discretion of the study PI depending on the severity of endoscopic finding at the time of removal and the clinical need based on best clinical guidelines and practices.

6.6 Management of Device Failure

If there is a device malfunction during the initial endoscopic placement (e.g. balloon is deflated, perforated, or other failure), then the balloon will be replaced with a new balloon during the same procedure.

During the follow-up visits or phone calls, if there is concern that the balloon is malfunctioning or may be deflated after successful placement, which can be suggested by the lack of satiety, ability to eat larger meals, or failure to lose weight during two consecutive follow-up visits, an abdominal ultrasound assessment will be performed.

- If the balloon is intact, then no endoscopic assessment will be indicated.
- If there is evidence of balloon malfunction without complication, a new balloon will be placed.
- If the balloon is deflated in the stomach, it will be replaced endoscopically with a new balloon.
- If the balloon is not in the stomach and subject has no symptoms of small bowel obstruction, the subject will be observed for 3 days for spontaneous passage of the balloon. Serial abdominal x-rays will be performed to monitor progression of the balloon in addition to clinical follow-up of signs and symptoms that may indicate a small bowel obstruction (e.g. pain, bilious vomiting, etc.) If the balloon doesn't pass, an attempt to remove it endoscopically will be performed. If not reachable by the endoscopy, the subject will be referred for surgical removal.

6.7 Removal of Balloon after 6 months by PI or Co-PI

The balloon will remain in the stomach if tolerated for 6 months, and then it will be removed endoscopically by a gastroenterologist (Dr. Absah or Dr. Abu Dayyeh). In order to prepare for the IGB removal, the subject will need to be on a liquid diet for 48 hours prior to its removal, and consume nothing by mouth for at least 12 hours prior to the IGB removal.

6.8 Schedule of Events

Table 2 provides a complete list of tests, procedures, and questions which will take place at each study visit, along with a time period and range for each study visit.

Table 2: Schedule of Events

Visit Type	Screening Visit	Baseline Visit	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Time Period	-4 weeks (+4 weeks)	-2 weeks (+2 weeks)	Day 0	4 days (± 1 day)	2 weeks (±1 week)	1 month (±1 week)	2 months (±1 week)	3 months (±1 week)	4 months (±1 week)	5 months (±1 week)	6 months (±1 week)	7 months (±1 week)	8 months (±1 week)	9 months (±1 week)	10 months (±1 week)	11 months (±1 week)	12 months (±1 week)
Inclusion & Exclusion Criteria	x																
Consent	x																
Psychological exam		x						x			x						x
Blood sample: GI hormones (2)		x						x			x			x			x
Stool sample (3)		x															
Urine pregnancy test (females) (4)			x														
EGD/IGB insertion (1,4)			x														
EGD/IGB removal (1,5)											x						
Other Blood & Urine samples (6)		x						x			x			x			x
PN Q (7)	x																x
CES-D & SCAS (7)	x							x									x
WMC		x						x			x			x			x
PE (8)		x	x					x			x			x			x
GI nurse telephone questionnaire				x	x	x	x		x	x		x	x		x	x	

Key:

EGD: upper endoscopy
IGB: Intragastric Balloon
PN Q: Pediatric Nutrition Questionnaire
CES-D: Self-Report Depression Scale Questionnaire
SCAS: Spence Child Anxiety Scale Questionnaire
WMC: Weight Management Clinic visit with dietitian
PE: Physical Exam by pediatric endocrinologist or pediatric gastroenterologist

Footnotes:

1-The IGB will be provided at no cost by the manufacturer.

2-GI hormones include: Total Ghrelin; PYY; GLP-1; and Leptin.

3-A stool sample will be collected for a fecal antigen study for H. pylori (sensitivity > 96.8%) to exclude the presence of H. pylori prior to the initial endoscopic assessment.

4-Female subjects will have a urine pregnancy test in the morning before the IGB insertion. Once the pregnancy test is confirmed negative, then the IGB can be inserted. At this visit, the subject will also be given a wallet card with emergency information, as well as Mayo Clinic brochures regarding the upper endoscopy and intragastric balloon for weight loss.

5-At the 6 month visit, the subject will have blood samples drawn; a physical exam by the pediatric endocrinologist (Dr. Kumar) or a pediatric gastroenterologist (Dr. Absah); and a meeting in the weight management clinic with the dietitian. Following the blood samples, PE, and WMC, the IGB will be removed at the same visit. The 6 month visit and balloon removal may all be completed in one day, or they may be completed on separate days depending on scheduling times and the subject's availability. This will be up to the discretion of the study team. In order to prepare for the IGB removal, the subject will need to be on a liquid diet for 48 hours prior to its removal, and consume nothing by mouth for at least 12 hours prior to the IGB removal.

6-Other tests include:

- CBC with differential
- Electrolytes panel (Sodium, Potassium, Calcium, Creatinine, Chloride, Bicarbonate, BUN)
- Liver function tests (AST, ALT, Alkaline phosphatase, Total Bilirubin, Total Protein, Albumin)
- Nutritional assessment (Fe/TIBC, B12, Folic Acid, 25-Hydroxy Vitamin D, Ferritin)
- Coagulation panel (ProTime/INR, PTT)
- Total Cholesterol/Lipid panel

- Thyroid function tests, PTH
- Insulin
- Glucose
- CRP
- HgA1c
- Urine sample

7-Questionnaires will be given to the subject after consenting to complete at home with a request that they be returned at the baseline visit. The PN Q will be returned to and reviewed by the dietitian at the weight management clinic. The CES-D and SCAS will be returned to and reviewed by the psychologist during the subject's psychological assessment. Any elevations in the CES-D and SCAS surveys will be further assessed during the subject's visit with the psychologist. If clinically indicated, additional psychological assessment and follow-up that may be needed and will be part of the subject's standard of care.

8-At the PE, the subject's height, weight, waist circumference, HR, BP, and demographics will be collected at baseline, 3, 6, 9 , and 12 months.

7 Statistical Plan

This is a pilot study of 12 subjects only, so results will be largely descriptive. Standard statistical analysis will be performed. We will use t-tests or alternative measures will be used to test whether weight loss was significant from baseline to each of the follow up points.

8 Safety and Adverse Events

All adverse events occurring during the study, including those not meeting the criteria of an Unanticipated Adverse Device Effect (UADE) will be recorded on the appropriate case report form. Records of these events will be maintained and reports submitted to the FDA and IRB according to the regulatory requirements. All adverse events will be reported. Expected clinical adverse events and anticipated adverse device effects are those listed in Section 1.5.2.

8.1 Definitions

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

Adverse Effect (Event)
Any untoward medical occurrence in a subject involved in clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study related treatment(s).

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as an unanticipated adverse device effect unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the local investigator should instruct each subject to report, to the local investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The local investigator should notify the study regulatory sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the local investigator should become aware of the development of problems, cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets all of the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**

- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined from enrollment in the study to 6 months after balloon removal (12 months from balloon insertion). Adverse events will be captured and reported from enrollment to the end of the study treatment follow-up.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Study subjects will be routinely questioned about adverse effects at study visits. Information on all adverse events should be recorded immediately in the source document, and also in the adverse event log. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of the treatment group if applicable or suspected causal relationship to the investigational device or if applicable other study treatment or diagnostic product(s) will be recorded in the subjects' case history. For all adverse effects sufficient information will be pursued and or obtained as to permit; an adequate determination of the outcome, an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable other study treatment or diagnostic product. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

Adverse events will be solicited at each study visit or contact with patient. All adverse events will be recorded with the following information:

- Subject Study Number/Identifier
- Device information (model and serial number)
- Date of event onset
- Description of the event
- Indication if study treatment was discontinued, or if investigational device was removed
- Subject current status, or if the event was resolved
- Principal Investigator assessment of if the event was serious and justification for determination
- Principal Investigator assessment of causality and relationship to study treatment.

8.3 Sponsor-Investigator Reporting of Unanticipated Adverse Device Effects and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

The sponsor-investigator will promptly review documented Unanticipated Adverse Device Effects and as necessary shall report the results of such evaluation to FDA within 10 working days and Mayo IRB within 5 working days of initial notice of the effect. Thereafter the sponsor-investigator will submit such additional reports concerning the effect as requested.

8.3.1 Sponsor-Investigator Reporting, Notifying Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

8.3.2 Sponsor-Investigator Reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unanticipated adverse device effects according to the required reporting timelines, formats and regulations.

The sponsor-investigator will submit a completed FDA Form 3500A to the FDA's Center for Devices and Radiological Health for any observed or reported adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to the DSMB and all participating sub-investigators.

The completed FDA Form 3500A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation shows that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the sponsor-investigator will submit a completed FDA Form 3500A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of any previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor-investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

Reporting Process
Unanticipated Adverse Device Effect reports will be submitted on FDA Form 3500A. The contact information for submitting reports is:

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Deviations from the investigational plan.

The sponsor-investigator shall notify Mayo IRB (see 21 CFR 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor-investigator is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB notification in accordance with 21 CFR 812.35(a) also is required.

8.4 Unblinding Procedures (Breaking the Blind) (as necessary if the study is blinded)

Not applicable

8.5 Stopping Rules

- 1 death
- 1 severe anticipated adverse event, including but not limited to:
  - Esophageal or gastric perforations
  - Peptic ulcer related bleeding requiring transfusion
  - Balloon deflation resulting in small bowel obstruction
  - Severe dehydration
  - Persistent vomiting and retching causing esophageal perforation requiring hospitalization
- 1 severe unanticipated adverse event, including but not limited to:
  - Any complication required more than 3 days of hospitalization
  - Any surgical intervention
  - Any admission to the Intensive Care Unit

8.6 Medical Monitoring

It is the responsibility of the sponsor-investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 10 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Internal Data and Safety Monitoring Board

Three independent consultants (two gastroenterologists-Dr. Bartlett and Dr. Topazian, and one endocrinologist-Dr. Lteif) at Mayo Clinic in Rochester will be the independent data safety and monitoring committee (DSMC) for this study.
The DSMB is charged with reviewing all study data and adverse events on a quarterly basis, and reporting on its findings. In addition the DSMB will be immediately notified of all UPIRTSOs and serious adverse events (whether or not they are anticipated) and will review these within one week of their occurrence.
The DSMB is authorized to suspend trial enrollment and device placement pending IRB and/ or FDA review if any of the following occur:
1) Any serious adverse event including death or other events requiring hospitalization or surgery.
2) A pattern of adverse events that in the opinion of the DSMB exceeds expected frequency or severity.
In addition the DSMB may, in coordination with the IRB and/or FDA, recommend device removals if appropriate.

8.6.2 Independent Data and Safety Monitoring Board

Not applicable

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records,

recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

9.3 Case Report Forms

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study, indicating the subject meets inclusion/exclusion criteria. The PI or co-investigator will review, approve and sign/date the completed CRF; the signature serves as attestation of his/her responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

Data Management

A database will be maintained by the study coordinator in order to ensure all data from each study visit is captured. This database will be stored on a secure Mayo Clinic computer and not be accessible to anyone outside the institution. Data abstracted from the subject's electronic medical record (EMR) will be input directly to the database without being copied to a CRF first. This database will not be shared with any persons outside of the Mayo Clinic institution.

Table 3: Source Document Map

Data Type	Source
Inclusion/Exclusion Criteria, including urine test results for pregnancy	CRF, based on EMR
Demographic data	EMR
Physical Exam & WMC visit	EMR
Blood, Urine, Stool test results	EMR
Psychological Exam	EMR
PN Q, CES-D, SCAS	Paper surveys completed by subject and returned to dietitian (PN Q) and psychologist (CES-D and SCAS)
GI nurse phone call results	Telephone questionnaire answered by subjects and their parents
Adverse Events	EMR and/or telephone questionnaire

Data Processing

The study coordinator will be responsible for gathering the required data at each study visit. The study coordinator will access the subject's EMR to obtain the required data from the study visits as indicated in Table 3 to enter directly into the study database as needed. The study coordinator will also obtain the PN Q from the dietitian at baseline and month 12. The study coordinator will obtain the CES-D and SCAS from the psychologist at baseline, month

3 and 12. In addition, the study coordinator will obtain the completed phone questionnaires from the GI nurse at 4 days, 2 weeks, and months 1, 2, 4, 5, 7, 8, 10, and 11. Adverse events will be maintained in a separate database.

Data Security and Confidentiality

Any study data with identifiers will be kept in a locked file cabinet or room and stored electronically on a password protected server.

Data Quality Assurance

Source documents will be verified to ensure they align with case report form data.

Data Clarification Process

Not applicable

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for:

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717, whichever is longer.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

As a service to the sponsor-investigator, this study will be monitored during the conduct of the trial by staff from the Mayo Clinic Office of Research Regulatory Support. Clinical trial monitoring may include review of the study documents and data generated throughout the duration of the study to help ensure the validity and integrity of the data along with the

protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

The sponsor-investigator will provide periodic progress reports to the FDA every six months.

10.2 Auditing and Inspecting

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as a sponsor-investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All adolescents interested in participating in this study and their parents/guardians will be provided with the consent form describing this study, supporting patient education materials about IGB placement and postoperative care including diet, and sufficient time to review those documents and ask questions. If the adolescent wishes to participate and parent agrees, the parent will be invited to sign the consent form indicating his/her consent for their adolescent to participate, and the adolescent will be invited to sign a separate line on the consent form indicating his/her assent. The consent form and supporting documents will be submitted with the protocol for review and approval by the IRB for the study. The consent form must be signed and dated by the participant and participant's legally authorized representative (i.e., parent or legal guardian) and the individual obtaining the informed consent and assent.

12 Study Finances

12.1 Funding Source

This study will be funded by the Mayo Clinic Children's Research Center. Apollo Endosurgery will be supplying the Orbera™ Intragastric Balloon at no charge.

12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

12.3 Subject Stipends or Payments

None

13 Publication Plan

This is an investigator initiated and funded study. The investigator holds the primary responsibility for publication. The trial will be registered on ClinicalTrials.gov prior to subject recruitment and enrollment. The results will also be posted to ClinicalTrials.gov within 12 months of final data collection for the primary outcome.

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15 Attachments

15.1 Appendix A – Female Birth Control Options

If the subject is sexually active and able to become pregnant, she must agree to use one of the birth control methods listed below:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

She must use birth control for the entire study and for at least 1 year after IGB placement.

If the female subject is using birth control at the time of the screening, this will be documented. If the female subject decides to be sexually active during the trial, then she will be required to

discuss her contraception measures, including risks and benefits, with her primary care provider. If she chooses to be placed on oral contraceptives, the primary care provider will ensure s/he has discussed and the subject understands the potential risk factors which will be document in the subject's medical records.