ORBERA® Intragastric Balloon System (ORBERA®)

Directions for Use (DFU)

Rx Only

Apollo Endosurgery, Inc.

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY

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1 INTRODUCTION

The information below is generalized. Each patient must be individually evaluated for the ORBERA Intragastric Balloon (ORBERA®) (referred to as IGB throughout this document) treatment based on the medical judgment of a qualified bariatric medical team.

Each physician and patient should evaluate the risks associated with endoscopy and intragastric IGBs and the possible benefits of a temporary treatment for weight loss prior to use of the IGB.

Physicians placing an IGB must fulfill the following requirements:

- Advanced upper endoscopy skill and experience evidenced by possession of Interventional Endoscopy privileges granted locally by the participating hospital or ambulatory facility.
- Completion of an Apollo Endosurgery sponsored or authorized comprehensive IGB training program.
- Clinical use of the IGB to make it a component of a multidisciplinary weight management practice which provides long-term support and follow-up.
- Have a comprehensive therapeutic weight management patient support program that includes appropriate endoscopy facilities, nutrition and exercise counseling, psychological, general medicine, and radiological support personnel.
- Able to have in-service training for support staff by Apollo Endosurgery trained product specialists.

Please see the last page for directions on obtaining additional information.

2 INFORMATION THAT SHOULD BE PROVIDED TO THE PATIENT

IGB placement is an elective procedure and the patient must be well counseled on the risk-benefit relationship. The physician must inform the patient of the warnings, precautions, and adverse events listed in this document. The physician should advise the patient that data from the ORBERA pivotal study is not an adequate representation of the U.S. patient population, as most of the patients were female and Caucasian. Data from this study may not accurately demonstrate the same effectiveness and safety profile in Hispanic, African American, or other ethnic populations. The physician should also advise the patient that early removal of the IGB may be required if serious adverse reactions occur.

3 DEVICE DESCRIPTION

ORBERA Intragastric Balloon (IGB) (Figure 1) is designed to assist weight loss by partially filling the stomach.

Figure 1: ORBERA filled to 400 cc and 700 cc with unfilled system in the foreground

The IGB is placed in the stomach and filled with sterile saline, causing it to expand into a spherical shape (Figure 2). The filled IGB is designed to occupy space and move freely within the stomach. The expandable design of the IGB permits a fill volume range of 400cc (minimum) to a maximum of 700cc (refer to the “Filling Recommendations” section). Once filled, the IGB volume is not adjustable. A self-sealing valve permits detachment from a Placement Catheter (see the “Directions for Use” Section).

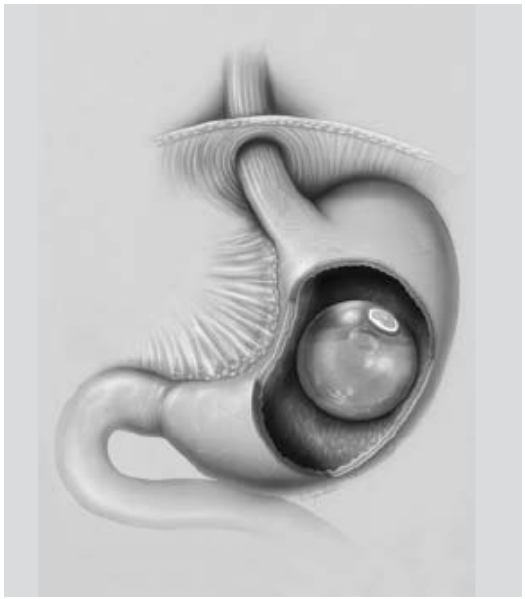

Figure 2: Saline-filled IGB in the stomach

The IGB is positioned within the “Placement Catheter Assembly” (Figure 3) which consists of a 6.5mm external-diameter catheter with length markers provided as a reference. One end of the catheter is connected to a sheath which houses the collapsed IGB and the opposite end has a Luer lock connector which allows the catheter to be attached to the “Fill Kit”. The tubing of the placement catheter is made of either silicone or polyurethane. Silicone catheters have a stainless-steel guidewire inserted into the catheter tubing for increased rigidity during placement. A guidewire is not present within polyurethane catheters as the rigidity of the material makes a guidewire unnecessary.

A ”Fill Kit” consisting of an IV spike, fill tube and filling valve is also provided to assist with the IGB filling process (Figure 4).

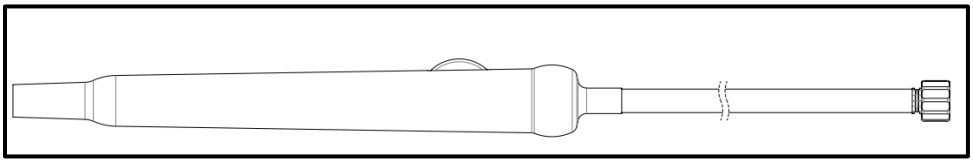

Figure 3: Placement Catheter Assembly (i.e. Sheath Assembly)

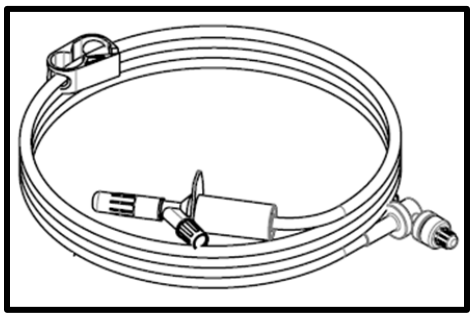

Figure 4: Fill Kit with IV Spike

4 INDICATIONS FOR USE

The ORBERA Intragastric Balloon System is indicated for use as an adjunct to weight reduction for adults with obesity with Body Mass Index (BMI) of ≥ 30 and ≤ 40 kg/m^2 and is to be used in conjunction with a long-term supervised diet and behavior modification program designed to increase the possibility of significant long-term weight loss and maintenance of that weight loss. ORBERA is indicated for adult patients who have failed more conservative weight reduction alternatives, such as supervised diet, exercise and behavior modification programs. The maximum placement period for ORBERA is 6 months.

5 PRODUCT SPECIFICATIONS

- ORBERA System, Reference No. B-4800 (IGB positioned in a Placement Catheter Assembly (i.e. sheath assembly))
- The IGB System contains no latex or natural rubber materials.
- The products are supplied clean, non-sterile and packaged for single use.
- The materials used to fabricate this device (see Table 1) have been tested according to ISO 10993, the international Standard for biological evaluation of medical devices.

Table 1: IGB Product Materials

System Component	Materials
IGB	Silicone elastomer components coated in Sodium Bicarbonate
Placement Catheter Assembly	**Tubing:** • Silicone (assemblies with a PTFE coated stainless-steel guidewire) • Polyurethane (assemblies without a PTFE coated stainless-steel guidewire) **Catheter Tip:** Polypropylene **Sheath:** Silicone elastomer and Silicone adhesive/primer coated in Sodium Bicarbonate

6 CONTRAINDICATIONS

Contraindications for use of the IGB System include:

- The presence of more than one IGB at the same time.
- Prior surgery involving the esophagus, stomach, and duodenum or bariatric surgery.
- Any inflammatory disease of the gastrointestinal tract including esophagitis, gastric ulceration, duodenal ulceration, cancer or specific inflammation such as Crohn's disease.
- 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.
- A large hiatal hernia of > 5cm or a hernia ≤ 5 cm with associated severe or intractable gastro-esophageal reflux symptoms.
- A structural abnormality in the esophagus or pharynx such as a stricture or diverticulum that could impede passage of the delivery catheter and/or an endoscope.
- Achalasia, symptoms suggestive of delayed gastric emptying, or presence of any other severe motility disorder that that may pose a safety risk during placement or removal of the device.
- Gastric Mass.
- Severe coagulopathy.
- Hepatic insufficiency or cirrhosis involving
  - Acute liver failure and advanced cirrhosis with encephalopathy muscle wasting and anasarca
  - Large esophageal varices with red color signs and gastric varices.
  - Severe portal hypertensive gastropathy with or without gastric antral vascular ectasia
- Patients who are known to have or suspected to have an allergic reaction to materials contained in the IGB
- Any other medical condition that would not permit elective endoscopy such as poor general health or history and/or symptoms of severe renal, hepatic, cardiac, and/or pulmonary disease.

- Serious or uncontrolled psychiatric illness or disorder that could compromise patient understanding of or compliance with follow up visits and removal of the device after 6 months.
- Alcoholism or drug addiction.
- Patients who are unable or unwilling to take prescribed proton pump inhibitor medication for the duration of the device implant.
- Patients unwilling to participate in an established medically-supervised diet and behavior modification program, with routine medical follow-up.
- Patients receiving aspirin, anti-inflammatory agents, anticoagulants, or other gastric irritants, not under medical supervision.
- Patients who are known to be pregnant or breast-feeding.

7 WARNINGS

- Proper positioning of the Placement Catheter Assembly and the IGB within the stomach (using measured distance from the incisors via the insertion tube markings) is necessary to allow proper filling. Lodging of the IGB in the esophageal opening during filling may cause serious injury. Failure to confirm proper positioning may cause injury to the esophagus, duodenum, or pylorus.
- When filling the IGB during the placement procedure, avoid rapid fill rates as these will generate high pressure which can damage the IGB valve or cause premature detachment of the IGB from the tip of the placement catheter.
- Each patient must be monitored closely during the entire term of treatment in order to detect the development of possible adverse events. Each patient should be instructed regarding symptoms of deflation (i.e. collapse), gastrointestinal obstruction, ulceration, gastric and esophageal perforation, acute pancreatitis, IGB inflation after placement (i.e. spontaneous hyperinflation) and other adverse events which might occur and should be advised to contact his/her physician immediately upon the onset of such symptoms. Patients need to be evaluated and the device removed at or within 6 months of placement.
- Patients with an IGB that present with severe abdominal pain that have a negative endoscopy and x-ray may additionally require a CT scan to definitively rule out a perforation.
- Patients must be advised that the IGB is intended to be placed for 6 months maximally, at which point removal is required. Longer periods of IGB placement increase the risk of IGB deflation (a reduction in size of the device due to loss of saline) which can lead to intestinal obstruction and risk for death. The risk of these events is also significantly higher when IGBs are filled to a larger volume than indicated (greater than 700cc).
- Bowel obstructions have been reported due to deflated (i.e. collapsed) IGBs passing into the intestines and have required surgical removal. The risk of intestinal obstruction may be higher in patients who have a dysmotility disorder, or who have had prior abdominal or gynecological surgery, radiation therapy, and/or active inflammatory bowel disease, so this should be considered in assessing the risk of the procedure. Bowel obstructions can result in death.
- Deflated devices should be removed promptly. Patients should be advised that IGB deflation may lead to serious adverse events including bowel obstruction and need for emergency surgery. Patients should immediately call their physician to receive instructions on preparing for removal of the IGB.
- Patients reporting loss of satiety, increased hunger and/or weight gain should be examined endoscopically as this is indicative of an IGB deflation.
- If it is necessary to replace an IGB that has spontaneously deflated (i.e. collapsed), fill the replacement IGB with the same volume of sterile saline that was used during the placement of previous IGB (i.e. initial fill volume). A greater initial fill volume in the replacement IGB may result in severe nausea, vomiting or ulcer formation.

- Acute pancreatitis has been reported as a result of injury to the pancreas by the IGB. Patients experiencing any symptoms of acute pancreatitis should be counseled to seek immediate care. Symptoms may include nausea, vomiting, abdominal or back pain, either steady or cyclic. If abdominal pain is steady, pancreatitis may have developed.
- Spontaneous hyperinflation of an indwelling IGB with gas has been reported in patients with indwelling ORBERA IGBs. Symptoms of significant IGB over-inflation include intense abdominal pain, swelling of the upper abdomen (abdominal distension) with or without discomfort, difficulty breathing, gastroesophageal reflux, nausea and/or vomiting. Patients experiencing any of these symptoms should be counseled to seek immediate care and should be evaluated for hyperinflation, particularly when persistent abdominal pain, abdominal distension, and food intolerance occur beyond the initial accommodative period of the balloon. Plain radiographic films will often demonstrate hyperinflation with a large air-fluid level within the balloon and an increase in IGB volume compared to the original volume
- Hyperinflation of the IGB often warrants its early removal to prevent serious complications such as gastric outlet obstruction and contact ulceration. Because hyperinflation increases the internal pressure of the IGB (due to accumulated gas) and may increase the fragility of the IGB wall, there is an increased risk of rupture followed by the sudden forceful release of gas and fluid contents when it is punctured or endoscopically manipulated. Therefore, it is suggested that the patient's airway is protected with endotracheal intubation prior to endoscopic removal in order to prevent pulmonary aspiration of the balloon contents. Additionally, in situations in which controlled balloon aspiration is done, it is recommended that mid-stream fluid aspirated from the balloon is sent for bacterial and fungal cultures.
- Pregnancy or breast-feeding contraindicates use of this device. Should pregnancy be confirmed at any time during the course of treatment, the device should be removed as soon as it is safely possible.
- Endoscopic removal of the IGB must be completed in the presence of an empty stomach. Patients should be on a liquid diet for 72 hours and NPO (i.e. nothing by mouth) for a minimum of 12 hours prior to removal. If food is found in the stomach upon endoscopic examination, then measures (aspiration of stomach contents, endotracheal intubation, or delay of procedure) must be taken to protect the airway. The risk of aspiration of gastric contents into the patient's lungs represents a serious risk which can result in death. Intragastric balloons have been shown to cause delayed gastric emptying which may increase the time typically needed to ensure an empty stomach prior to endoscopic procedures.
- The IGB is composed of a soft silicone elastomer and is easily damaged by instruments or sharp objects. The IGB must be handled only with gloved hands and with the instruments recommended in this document.

8 PRECAUTIONS

- When filling the balloon, the use of sterile saline and aseptic technique, similar to changing IV fluids (e.g. use of clean or sterile gloves, sterile syringe, etc.), is recommended. Though the cause of hyperinflation is unknown, it may be caused by fungal or bacterial microbes contaminating the balloon. One recommended mitigation is to avoid contaminating the saline within the balloon with micro-organisms that may lead to spontaneous hyperinflation.
- If difficulty with the IGB Placement Catheter is noted during placement (e.g., resistance to IGB filling), then the device should be removed and replaced with a new IGB. To lessen, or prevent catheter defects, the catheter must remain slack during the filling process. If the catheter is under tension during this process, the tip of the catheter may dislodge from the IGB, preventing further IGB deployment.
- Placement of the IGB within the stomach has been shown to produce a delay in gastric emptying. This can create a variety of expected and predictable reactions including a feeling of heaviness in the abdomen, nausea and vomiting, gastroesophageal reflux, belching, esophagitis, heartburn, diarrhea and, at times, abdominal, back or epigastric pain and cramping. Food digestion may be slowed throughout the entire placement duration due to the delay in gastric emptying. Most patients acclimate to the presence of the device within the first 2 weeks. In order to prevent or ameliorate the symptoms most frequently experienced after placement, physicians should prescribe proton pump inhibitors (PPIs) and antiemetics prophylactically and consider prescribing temporarily antispasmodics or anticholinergic medications for cramping due to accommodation of the IGB, and/or prokinetic medications for symptoms due to the delay in gastric emptying. Patients should be advised to immediately contact their physician for any unusually severe, worsening, or recurrent symptoms as these medications can further delay gastric emptying and may lead to stomach distention, perforation and possibly death.
- To prevent ulcers and control gastroesophageal reflux symptoms, it is recommended that the patient start a program of oral proton pump inhibitors (PPIs) for approximately 3-5 days prior to IGB placement so a maximal gastric acid suppression effect will be present on the day of placement. It is recommended that the PPI dose be given sublingually after IGB placement if nausea and/or vomiting are present. A starting full dose daily regimen of an oral PPI should be continued as long as the IGB is in place. Other medications that are started prophylactically should be continued after IGB placement until they are no longer needed. Furthermore, subjects will be directed to avoid medications known to cause or exacerbate gastroduodenal mucosal damage.
- The IGB is made of silicone elastomer which may be degraded by gastric acid. Physicians have reported that the concurrent use of medications, such as proton pump inhibitors, may reduce acid formation or reduce acidity, which can prolong the integrity of the IGB reduce the risk of device deflation) and may help to reduce the risk of gastric ulcers and subsequent perforation.
- The physiological response of the patient to the presence of the IGB may vary depending upon the patient's general condition and the level and type of activity. The types and frequency of administration of drugs or diet supplements and the overall diet of the patient may also affect the response.
- The use of the IGB has not been studied in individuals who have a patulous pylorus, active H. pylori infection, and subjects with either symptoms or a diagnosis of delayed gastric emptying.
- Patients taking anti-cholinergic medications or psychotropic medications should be informed that these medications will delay gastric emptying and should be used sparingly as they may put them at greater risk for stomach distention and perforation. Patients should be advised to immediately contact their physician for any unusually severe, worsening or recurrent symptoms.
- A patient whose deflated (i.e. collapsed) IGB has moved into the intestines must be monitored closely for an appropriate period of time (at least 2 weeks) to confirm its uneventful passage through the intestine.

- In preparation for removal, some patients may have retained contents in the stomach. Some patients may have a clinically significant delay in gastric emptying and refractory intolerance to the IGB, necessitating early removal, and possibly leading to other adverse events. These patients may be at higher risk of aspiration upon removal and/or upon administration of anesthetic. The anesthesia team should be alerted to the risk for aspiration in these patients.

9 RISK ASSOCIATED WITH RE-USE

The IGB System is for single use only. Removal of the IGB requires that it be punctured in situ to deflate, and any subsequent reuse would result in the IGB deflating in the stomach. This could lead to possible bowel obstruction and may require surgery to remove. Should an IGB be removed from the patient prior to being filled with saline, it still cannot be reused on a new patient as any attempt to decontaminate this device could cause damage resulting again in deflation after implantation.

10 ADVERSE EVENTS

It is important to discuss all possible adverse events with your patient. Adverse events that may result from the use of this product include the risks associated with the medications and methods utilized in the endoscopic procedure, the risks associated with any endoscopic procedure, the risks associated with the IGB specifically, and the risks associated with the patient's degree of intolerance to a foreign object placed in the stomach.

NOTE: Any serious incident that has occurred in relation to the device should be reported to Apollo Endosurgery (see contact information at the end of this document) and any appropriate government entity.

10.1 Possible Adverse Events

Possible adverse events associated with the use of the IGB include:

- Death due to complications related to aspiration, intestinal obstruction, gastric perforation, or esophageal perforation, is possible.
- Intestinal obstruction by the IGB. An insufficiently filled IGB or a leaking IGB that has lost sufficient volume may be able to pass from the stomach into the small bowel. It may pass all the way into the colon and be passed with stool. However, if there is a narrow area in the bowel or adhesion formation, which may occur after previous surgery on the bowel, the IGB may not pass and could cause a bowel obstruction. If this occurs, surgery or endoscopic removal could be required.
- Esophageal obstruction. When the IGB is being filled in the stomach, the IGB could be inadvertently pulled back into the esophagus. If this occurs, surgery or endoscopic removal could be required.
- Gastric outlet obstruction. A partially-filled IGB (i.e., <400cc), or a leaking IGB could lead to gastric outlet obstruction, requiring IGB removal. It is also possible for a fully filled (400-700cc) IGB to impair the gastric outlet, which can produce a mechanical impediment to gastric emptying. Gastric outlet obstruction may require early removal.
- Gastric distention with retained food and fluid due to severely delayed gastric emptying with or without outlet obstruction from displacement of the IGB into the antrum.
- Injury to the digestive tract during placement of the IGB in an improper location such as in the esophagus or duodenum. This could cause bleeding and perforation, which could require a surgical or endoscopic correction for control.

- Insufficient or no weight loss.
- Adverse health consequences resulting from weight loss.
- Gastric discomfort, feelings of nausea and vomiting following IGB placement as the digestive system adjusts to the presence of the IGB.
- Continuing nausea and vomiting. This could result from direct irritation of the lining of the stomach, delayed gastric emptying and/or the IGB blocking the outlet of the stomach. It is even theoretically possible that the IGB could prevent vomiting (not nausea or retching) by blocking the inlet to the stomach from the esophagus.
- 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 IGB. Rapid release of this fluid into the intestine could cause infection, fever cramps and diarrhea.
- Injury to the lining of the digestive tract as a result of direct contact with the endoscope, the IGB, grasping forceps or as a result of increased acid production by the stomach. This could lead to ulcer formation with pain, bleeding or even perforation. Surgery could be necessary to correct this condition.
- Death due to complications related to gastric or esophageal perforation is possible.
- IGB deflation (i.e. collapse) and subsequent replacement.
- Acute pancreatitis.
- Spontaneous hyperinflation due to gas production within the IGB.

10.2 Possible Complications of Routine Endoscopy & Sedation

Potential risks associated with upper endoscopic procedures include, but are not limited to: abdominal cramping and discomfort if air used to distend the stomach, sore or irritated throat, bleeding, infection, tearing of the esophagus or stomach that could lead to perforation, and aspiration pneumonia. The risk increases if additional procedures are performed.

According to the American College of Gastroenterology, risks related to sedation during endoscopic procedures are rare, occurring in less than one in every 10,000 people.[1] The most common complications involve a temporary decrease in the rate of breathing or heart rate, which can be corrected by giving extra oxygen or by reversing the effect of the sedative medications. Patients with heart, lung, kidney, liver, or other chronic diseases are at higher risk for complications. Drug dosages and airway management should be taken into consideration when treating high risk patients.

11 CLINICAL EVALUATION OF THE ORBERA INTRAGASTRIC BALLOON SYSTEM

In the randomized, controlled clinical trial to evaluate the safety and effectiveness of the ORBERA Intragastric Balloon System (ORBERA), 125 subjects randomized to the treatment group and 35 subjects in the run-in group had the ORBERA endoscopically placed. The run-in group included mentored, non-randomized cases in order for physicians to gain experience with ORBERA placement and removal procedures. Each run-in subject had an IGB placed, removed, and another IGB placed. In all subjects the IGB was left in place for a maximum of 6 months. All ORBERA subjects participated in a concurrent behavioral modification program for 12 months: the first 6 months while ORBERA was

in place and another 6 months after the device had been removed. The study design and effectiveness results are presented in section 11(Clinical Studies).

There were no unanticipated adverse device effects or deaths reported during the pivotal study. Sixteen (16) ORBERA-treated subjects had a total of 17 device or procedure-related serious adverse events[1] (SAEs) resulting in an SAE rate of 10% (16/160, 95% CI). Eleven subjects in the treatment group experienced 12 device-related serious adverse events SAEs. Two (2) subjects in the treatment group experienced a procedure-related SAE. Two (2) subjects in the run-in group experienced 2 device-related SAEs, and two (2) run-in subjects experienced 2 procedure-related SAEs. All device and procedure-related SAEs in both the treatment and run-in groups resolved without sequelae.

30 out of 160 (18.8%) ORBERA-treated subjects had their IGB removed endoscopically prior to 6 months. 8 out the 30 were due to serious adverse events of device intolerance. Seven (7) out of 30 early removals were due to other AEs, but not diagnosed as device intolerance by the Investigator. There were 15 additional early removals which were due to subject request. No additional information is available for these subjects.

Cases of device intolerance were adjudicated by the Investigator and the sponsor's Medical Monitor and subsequently reviewed by an Independent Data Safety Monitoring Board (DSMB). The use of anticholinergic and antispasmodic drugs to treat gastrointestinal upset during the adjustment period was contraindicated under protocol Amendment 1 and the use of these medications was considered a protocol deviation. After a learning curve of how to manage the adjustment period, the protocol was amended, a definition of device intolerance was added, and the use of anticholinergic and antispasmodic drugs was allowed under protocol Amendment 2.

All 14 device-related SAEs that occurred in the U.S. pivotal study are included in Table 3. All 3 procedure-related SAEs that occurred in the U.S. pivotal study are included in Table 4. Serious adverse events observed in global product experience with ORBERA and from literature reviews, but not seen in the U.S. clinical study include: ulcerations/erosions, IGB deflation/migration, esophageal perforation, cardiac complications/cardiac arrest, and death.

Since the U.S. FDA approval, acute pancreatitis, spontaneous hyperinflation, and death have been reported in patients with ORBERA. These adverse events were not identified in the U.S. pivotal study. The reported occurrence rates in the United States for several of these events that were not seen in the U.S. pivotal study (as well as gastric perforation and aspiration, which were both observed once in the pivotal study) are shown in Table 2 below.

Table 2: Reported Occurrence Rates in the U.S. for Selected Adverse Events

Adverse Events	Count	Rate
Spontaneous Hyperinflation	62	0.374%
Gastric Perforation (Stomach Perforation)	15	0.090%
Acute Pancreatitis	13	0.078%
Aspiration	13	0.078%
Death	5	0.030%
Esophageal Perforation	3	0.018%
Total	**111**	**0.670%**
ORBERA (B-4800) Units Sold in United States from August 05, 2015 (PMA) through March 30, 2020	**16,579**	

† Some complaints were counted in multiple categories due to multiple events being reported in one complaint The above numbers do not indicate number of devices nor patients involved. Includes complaints reported against unknown catalogs. Does not include non-device related events.
†† Rate calculations are based on total number of devices distributed, which may be greater than the number of devices placed.

Table 3: All device-related Serious Adverse Events that occurred in the U.S. Pivotal Study, which required hospital stay or were deemed to be important medical events (N=160)

Device-Related Serious Adverse Event[1]	Number of subjects out of 160[2] (% of subjects)	Number of Events	Onset (days to event)	Number of subjects with event that had device removed (% of subjects with device removal)
Device Intolerance[3]	8 out of 160 (5%)	8	Mean = 1 day Median = 1 day Range = 1-15 days	8/8 (100%)
Dehydration	2 out of 160 (1.3%)	2	Mean = 1.5 days Median = 2 days Range = 1-3 days	2/2 (100%) (1 subject had device intolerance in addition to dehydration)
Gastric outlet obstruction with moderate diffuse gastritis	1 out of 160 (.63%)	1	24 days	1/1 (100%)
Gastric perforation with sepsis	1 out of 160 (.63%)	1	3 days	1/1 (100%)
Aspiration pneumonia	1 out of 160 (.63%)	1	74 days	1/1 (100%)
Abdominal cramping and infection (fluid inside IGB positive for *Candida albicans*)	1 out of 160 (.63%)	1	154 days	1/1 (100%)

1. A serious adverse event is one that:
   - Led to death,
   - Led to a serious deterioration in the health of a patient that:
     - Resulted in a life-threatening illness or injury,
     - Resulted in a permanent impairment of a body function or body structure,
     - Required in-patient hospitalization or prolonged hospitalization,
     - Resulted in medical or surgical intervention to prevent permanent impairment to a body function or body structure,
     - Led to fetal distress, fetal death or a congenital abnormality or birth defect.
2. 125 randomized subjects plus 35 run-in subjects = 160 subjects at risk. Run-in subjects received 2 device placements and 1 removal on the same day, and then the 2nd device was planned for removal at 6 months. Run-in subjects were mentored cases which were enrolled prior to randomized subjects in order for physicians to gain experience placing and removing ORBERA
3. Device Intolerance is defined as severe and intolerable symptoms of gastrointestinal upset (i.e., nausea, vomiting, reflux, pain) which led device removal prior to 6 months

Table 4: All procedure-related Serious Adverse Events that occurred in the U.S. Pivotal Study (N=160)

Procedure-Related Serious Adverse Event[1]	Number of subjects out of 160[2] (% of subjects)	Number of Events	Onset	Treatment	Number of subjects with event that had device removed
Esophageal mucosal injury	2 out of 160 (1.3%)	2 (1 tear and 1 superficial dissection)	Tear: During IGB removal Dissection: During IGB placement	Tear and dissection: Hospitalization - injury resolved	0
Laryngospasm	1 out of 160 (.63%)	1	During IGB placement	Intubation	0

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   - Led to death,
   - Led to a serious deterioration in the health of a patient that:
     - Resulted in a life-threatening illness or injury,
     - Resulted in a permanent impairment of a body function or body structure,
     - Required in-patient hospitalization or prolonged hospitalization,
     - Resulted in medical or surgical intervention to prevent permanent impairment to a body function or body structure,
     - Led to fetal distress, fetal death or a congenital abnormality or birth defect.
2. 125 randomized subjects plus 35 run-in subjects = 160 subjects at risk. Run-in subjects received 2 device placements and 1 removal on the same day, and then the 2nd device was planned for removal at 6 months. Run-in subjects were mentored cases which were enrolled prior to randomized subjects in order for physicians to gain experience placing and removing ORBERA

The most common device-related gastrointestinal adverse events, occurring in >10% of ORBERA-treated subjects are included in Table 5.The most frequently occurring events were nausea (86.9% of subjects), vomiting (75.6% of subjects), generalized abdominal pain (57.5% of subjects), and gastroesophageal reflux disease (30% of subjects).

Table 5: All Gastrointestinal Device-Related Adverse Events occurring in >10% of ORBERA-treated Subjects in the Pivotal Study (N=160)

Adverse Event	Number of Subjects (% of Subjects) N=160	Day of Onset: Median (Mean) Range	Duration (in days): Median (Mean) Range	Severity: n/N (%): Mild[1] Moderate[2] Severe[3]	Number of subjects with onset ≤ 3 days post-placement (% of subjects)	% of subjects with onset ≤ Day 3 post-placement with duration > 14 days and <=30 days	% of subjects with onset ≤ Day 3 post-placement with duration > 30 days
Nausea	139 (86.9%)	0.00 (10.30) 0-180	3.00 (12.36) 0-181	73/139 (52.5%) 59/139 (42.4%) 7/139 (5.0%)	123 (88.5%)	6 (4.8%)	9 (7.2%)
Vomiting	121 (75.6%)	1.00 (13.29) 0-188	2.00 (7.66) 0-169	54/121 (44.6%) 61/121 (50.4%) 6/121 (5.0%)	103 (85.1%)	3 (2.9%)	4 (3.9%)
Abdominal pain (general)	92 (57.5%)	1.00 (20.34) 0-185	5.00 (10.95) 0-151	44/92 (47.8%) 43/92 (46.7%) 5/92 (5.4%)	74 (80.4%)	5 (6.8%)	4 (5.4%)
Gastro-esophageal reflux disease	48 (30.0%)	19.00 (42.29) 0-210	27.00 (51.00) 0-187	31/48 (64.6%) 12/48 (25%) 5/48 (10.4%)	16 (33.3%)	1 (6.3%)	7 (43,8%)
Eructation	39 (24.4%)	52.00 (64.87) 1-185	52.00 (83.00) 0-174	35/39 (89.7%) 4/39 (10.3%) 0/39 (0%)	4 (3.2%)	0 (0%)	3 (75.0%)
Dyspepsia	34 (21.3%)	39.50 (54.68) 0-169	24.00 (54.17) 0-180	24/34 (70.6%) 8/34 (23.5%) 2/34 (5.9%)	9 (7.2%)	0 (0%)	4 (44.4%)
Constipation	32 (20.0%)	14.00 (33.31) 0-223	12.00 (30.86) 0-186	29/32 (90.6%) 3/32 (9.4%) 0/32 (0%)	10 (8.0%)	2 (20.0%)	2 (20.0%)
Abdominal pain (upper)	29 (18.1%)	1.00 (34.62) 0-192	3.00 (11.15) 0-128	18/29 (62.1%) 11/29 (37.9%) 0/29 (0%)	20 (16.0%)	0 (0%)	0 (0.0%)
Abdominal distension	28 (17.5%)	26.00 (46.57) 0-167	6.00 (24.28) 0-174	24/28 (85.7%) 3/28 (10.7%) 1/28 (3.6%)	8 (6.4%)	2 (25.0%)	1 (12.5%)
Dehydration	23 (14.4%)	2.00 (7.35) 0-46	0.50 (2.95) 0-39	9/23 (39.1%) 11/23 (47.8%) 3/23 (13%)	16 (12.8%)	0 (0%)	1 (6.3%)
Diarrhea	21 (13.1%)	23.00 (72.10) 1-225	3.00 (14.38) 0-103	15/21 (71.4%) 6/21 (28.6%) 0/21 (0%)	3 (2.4%)	0 (0%)	0 (0.0%)
Flatulence	18 (11.3%)	27.50 (54.22) 3-198	32.00 (37.67) 0-125	14/18 (77.8%) 4/18 (22.2%) 0/18 (0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)

1. Mild = Awareness of sign or symptom, but easily tolerated
2. Moderate = Discomfort enough to cause interference with usual activity
3. Severe = Incapacitating with inability to work or do usual activity

A total of 606 device-related Adverse Events (AEs) were reported in the mITT population (n=125) and 204 in the Run-In group (n=35) for a total of 810 device-related AEs in the ORBERA-treated population (N=160). Use of anticholinergic and antispasmodic medications were prohibited under protocol Amendment 1; therefore, the frequency of AEs in the Run-In group was higher than the frequency of AEs in the mITT population. All device-related AEs occurring in the pivotal study are summarized in Table 6, listed in order of frequency of events. The majority of events were mild to moderate in severity and resolved within 2 weeks. Of the device-related AEs in the treatment group, 59.7% were considered mild, 34.5% were considered moderate and 5.8% of the AEs were categorized as severe. Of the device-related AEs in the run in- group, 36.7% were categorized mild, 19.1% considered moderate and 4.6% were categorized as severe.

Ninety-two (92) of the 130 control subjects (70.8%) experienced a total of 429 AEs, most of which were mild (309 events, 72.0%) or moderate (95 events, 22.1%). Twenty-four events (5.6%) were severe.

Table 6: All Device-Related Adverse Events in the ORBERA Group (N=160)

Preferred Terms	#Subjects with Events (% of Subjects)	#Events (Frequency %)	#Subjects with Event Occurrence >1 (% Occurrence)
Nausea	139 (86.8%)	139 (17.2%)	34 (21.3%)
Vomiting	121 (75.6%)	121 (14.9%)	33 (20.6%)
Abdominal pain	92 (57.5%)	92 (11.4%)	19 (11.9%)
Gastroesophageal reflux disease	48 (30.0%)	48 (5.9 %)	15 (9.4%)
Eructation	39 (24.4%)	39 (4.8%)	4 (2.5%)
Dyspepsia	34 (21.3%)	34 (4.2%)	13 (8.1%)
Constipation	32 (20.0%)	32 (3.9%)	3 (1.9%)
Abdominal pain (upper)	29 (18.1%)	29 (3.6%)	7 (4.4%)
Abdominal distension	28 (17.5%)	28 (3.5%)	3 (1.9%)
Dehydration	23 (14.4%)	23 (2.8%)	3 (1.9%)
Diarrhea	21 (13.1%)	21 (2.6%)	3 (1.9%)
Flatulence	18 (11.2%)	18 (2.2%)	2 (1.3%)
Impaired gastric emptying	14 (8.8%)	14 (1.7%)	0 (0%)
Abdominal discomfort	10 (6.3%)	10 (1.2%)	1 (0.6%)
Medical device complication[1]	9 (5.6%)	9 (1.1%)	0 (0%)
Asthenia	8 (5.0%)	8 (.98%)	0 (0%)
Headache	8 (5.0%)	8 (.98%)	0 (0%)
Post procedural pain	8 (5.0%)	8 (.98%)	0 (0%)
Fatigue	7 (4.4%)	7 (.86%)	1 (0.6%)
Halitosis	6 (3.8%)	6 (.74%)	0 (0%)
Abdominal rigidity	5 (3.1%)	5 (.62%)	1 (0.6%)
Dysphagia	5 (3.1%)	5 (.62%)	2 (1.3%)
Gastrointestinal pain	5 (3.1%)	5 (.62%)	2 (1.3%)
Pharyngolaryngeal pain	5 (3.1%)	5 (.62%)	0 (0%)
Vitamin B1 decreased	5 (3.1%)	5 (.62%)	0 (0%)
Hiccups	4 (2.5%)	4 (.49%)	0 (0%)
Esophagitis	4 (2.5%)	4 (.49%)	0 (0%)
Anorexia	3 (1.9%)	3 (.37%)	0 (0%)
Gastric outlet obstruction	3 (1.9%)	3 (.37%)	0 (0%)
Gastritis	3 (1.9%)	3 (.37%)	0 (0%)
Pneumonia	3 (1.9%)	3 (.37%)	0 (0%)
Retching	3 (1.9%)	3 (0.37%)	0 (0%)
Alopecia	2 (1.3%)	2 (0.37%)	0 (0%)
Anemia	2 (1.3%)	2 (0.25%)	0 (0%)
Anxiety	2 (1.3%)	2 (0.25%)	0 (0%)

Preferred Terms	#Subjects with Events (% of Subjects)	#Events (Frequency %)	#Subjects with Event Occurrence >1 (% Occurrence)
Back pain	2 (1.3%)	2 (0.25%)	0 (0%)
Cough	2 (1.3%)	2 (0.25%)	0 (0%)
Dizziness	2 (1.3%)	2 (0.25%)	0 (0%)
Epigastric discomfort	2 (1.3%)	2 (0.25%)	0 (0%)
Fecal incontinence	2 (1.3%)	2 (0.25%)	0 (0%)
Hypokalemia	2 (1.3%)	2 (0.25%)	0 (0%)
Intestinal spasm	2 (1.3%)	2 (0.25%)	1 (0.6%)
Migraine	2 (1.3%)	2 (0.25%)	0 (0%)
Non-cardiac chest pain	2 (1.3%)	2 (0.25%)	0 (0%)
Abdominal pain (lower)	1 (0.6%)	1 (0.12%)	0 (0%)
Atelectasis	1 (0.6%)	1 (0.12%)	0 (0%)
Blood creatinine increased	1 (0.6%)	1 (0.12%)	0 (0%)
Bronchitis	1 (0.6%)	1 (0.12%)	0 (0%)
Candidiasis	1 (0.6%)	1 (0.12%)	0 (0%)
Chills	1 (0.6%)	1 (0.12%)	0 (0%)
Device failure	1 (0.6%)	1 (0.12%)	0 (0%)
Diverticulitis	1 (0.6%)	1 (0.12%)	0 (0%)
Dyspepsia	1 (0.6%)	1 (0.12%)	0 (0%)
Dyspnea	1 (0.6%)	1 (0.12%)	0 (0%)
Dyspnea (exertional)	1 (0.6%)	1 (0.12%)	0 (0%)
Erosive esophagitis	1 (0.6%)	1 (0.12%)	0 (0%)
Excoriation	1 (0.6%)	1 (0.12%)	0 (0%)
Flushing	1 (0.6%)	1 (0.12%)	0 (0%)
Food intolerance	1 (0.6%)	1 (0.12%)	0 (0%)
Gastric infection	1 (0.6%)	1 (0.12%)	0 (0%)
Gastritis erosive	1 (0.6%)	1 (0.12%)	0 (0%)
Gastrointestinal motility disorder	1 (0.6%)	1 (0.12%)	0 (0%)
Hematochezia	1 (0.6%)	1 (0.12%)	0 (0%)
Hypertension	1 (0.6%)	1 (0.12%)	0 (0%)
Hypoesthesia	1 (0.6%)	1 (0.12%)	0 (0%)
Hypotension	1 (0.6%)	1 (0.12%)	0 (0%)
Hypotrichosis	1 (0.6%)	1 (0.12%)	0 (0%)
Hypoventilation	1 (0.6%)	1 (0.12%)	0 (0%)
Hypoxia	1 (0.6%)	1 (0.12%)	0 (0%)
Insomnia	1 (0.6%)	1 (0.12%)	0 (0%)
Lentigo	1 (0.6%)	1 (0.12%)	0 (0%)
Malaise	1 (0.6%)	1 (0.12%)	0 (0%)
Malnutrition	1 (0.6%)	1 (0.12%)	0 (0%)
Muscle spasms	1 (0.6%)	1 (0.12%)	0 (0%)
Nasal congestion	1 (0.6%)	1 (0.12%)	0 (0%)
Edema peripheral	1 (0.6%)	1 (0.12%)	0 (0%)
Esophageal candidiasis	1 (0.6%)	1 (0.12%)	0 (0%)
Esophageal hemorrhage	1 (0.6%)	1 (0.12%)	0 (0%)
Peritoneal candidiasis	1 (0.6%)	1 (0.12%)	0 (0%)
Peritonitis	1 (0.6%)	1 (0.12%)	0 (0%)
Pleural effusion	1 (0.6%)	1 (0.12%)	0 (0%)
Pneumoperitoneum	1 (0.6%)	1 (0.12%)	0 (0%)
Rash	1 (0.6%)	1 (0.12%)	0 (0%)
Regurgitation of food	1 (0.6%)	1 (0.12%)	0 (0%)
Sinusitis	1 (0.6%)	1 (0.12%)	0 (0%)
Tachycardia	1 (0.6%)	1 (0.12%)	0 (0%)

Preferred Terms	#Subjects with Events (% of Subjects)	#Events (Frequency %)	#Subjects with Event Occurrence >1 (% Occurrence)
Tachypnea	1 (0.6%)	1 (0.12%)	0 (0%)
Urine ketone body present	1 (0.6%)	1 (0.12%)	0 (0%)
Total		**810**	

1. Preferred term for device intolerance

12 CLINICAL STUDIES

12.1 ORBERA U.S. Pivotal Study

12.1.1 Pivotal Study Design

The pivotal study of ORBERA, known as IB-005, was a multicenter, prospective, randomized, non-blinded comparative study. Obese subjects with BMI ≥30 kg/m^2 and ≤ 40 kg/m^2 were randomized to ORBERA treatment or control in a 1:1 ratio. Study subjects randomized to the ORBERA treatment group underwent placement of ORBERA followed by ORBERA removal after 6 months (26 weeks). The ORBERA group concurrently participated in a 12-month behavioral modification program (i.e., 6 months with ORBERA in place plus 6 months after ORBERA was removed). The control group participated in the 12-month behavioral modification program alone. For subjects in the ORBERA group, the device was removed at Month 6, with regular office visits continuing through 1 year. All subjects had routine visits throughout the study to evaluate safety and effectiveness, with a total of 26 scheduled visits over the 1-year period.

12.1.2 Study Endpoints

With regards to effectiveness, there were two co-primary effectiveness measures:

1. The mean percent excess weight loss (%EWL) of the ORBERA group at Month 9 (3 months after device removal) with a performance goal of at least 25% EWL.

   H_0: $\mu_A \leq$ 25% EWL

   H_A: $\mu_A >$25% EWL

2. Responder rate of the treated subjects group was at least 30%, where a responder was defined as an ORBERA-treated subjects who attained at least ≥ 15% EWL over the mean %EWL of the control group.

   H_0: $P_A \leq 30\%$

   H_A: $P_A >30\%$

The study was successful if, at Month 9, the ORBERA group achieved at least 25% EWL, and if 30% of ORBERA-treated subjects had significantly greater weight loss than the control group. Percent EWL is defined as weight loss (screening weight minus selected weight) divided by excess weight (screening weight minus ideal weight) multiplied by 100. The 1983 Metropolitan Life Height and Weight Table was used to determine ideal weight for these co-primary effectiveness measures.

Secondary effectiveness endpoints included

1. The change in status of comorbid conditions of type 2 diabetes, hypertension, and dyslipidemia at Month 9, as measured by lab tests and vital signs
2. The change in quality of life at Month 9 as measured by the Impact of Weight on Quality of Life - Lite (IWQOL-Lite) and Short Form 36 (SF-36) questionnaires.

Additional effectiveness measures included these primary and secondary measures evaluated at different time points, including at Month 6 when the device was removed. Also included were changes from baseline in BMI, weight, percent total body weight loss (%TBWL), depressive symptoms and severity, eating behavior, and doses of concomitant medications prescribed to manage comorbidities.

Safety measures included the incidence and severity of adverse events related to treatment. An exploratory safety measure was the impact of the device on gastric emptying.

12.1.3 Subject Demographics

A total of 448 subjects were enrolled in the study: 131 were screen failures primarily due to ineligibility, 44 were run-in subjects, and 273 were randomized per protocol, 18 of whom discontinued prior to treatment. Of the remaining subjects, 125 were randomized to the treatment group and 130 were randomized to the control group. All results presented in this section reflect only those subjects who were randomized to the ORBERA or Control groups (i.e., 125 and 130, respectively).

More than three-fourths (78.4%, 98/125) of the treatment group and 71.5% (93/130) of the control group completed the full study at Week 52. Subjects in the ORBERA group were primarily female (89.6%, 112/125) and of Caucasian descent (80.8%, 101/125). Median age at study entry was 38.0 years (range, 19 to 60). Mean BMI was 35.2 kg/m^2. Subjects in the control group were also primarily female (90.0%, 117/130) and of Caucasian descent (81.5%, 106/130). Median age at study entry was 41.0 years (range, 20 to 62). Mean BMI was 35.4 kg/m^2. Key demographics and baseline characteristics are presented in Table 7.

Table 7: Subject Demographics and Baseline Characteristics (N = 255 Subjects)

Demographics[1]	Category	ORBERA (n = 125) n	ORBERA (n = 125) (%)	Control (n = 130) n	Control (n = 130) (%)
Gender	Female	112	89.6%	117	90.0%
	Male	13	10.4%	13	10.0%
Age (years)	18-19	1	0.8%	0	0
	20-21	2	1.6%	5	4.0%
	22-29	19	15.2%	13	10.4%
	30-39	49	39.2%	37	28.5%
	40-49	31	24.8%	54	41.5%
	50-59	22	17.6%	16	12.3%
	60 & over	1	0.8%	5	3.8%
	Mean (SD)	38.7 (9.37)		40.8 (9.61)	
	Median	38.0		41.0	
	Range	19, 60		20, 62	
	95% CI	37.09, 40.40		39.15, 42.48	
Race	Caucasian	101	80.8%	106	81.5%
	Hispanic	9	7.2%	7	5.4%
	Black (not of Hispanic origin)	14	11.2%	15	11.5%
	Asian	0	0	0	0
	Other	1	0.8%	2	1.5%
Excess Weight[2] (lbs.)	Mean (SD)	78.80 (24.328)		79.05 (19.555)	
	Median	75.20		78.30	
	Range	35.0, 151.3		39.4, 146.0	
	95% CI	74.491 , 83.105		75.658 , 82.445	
BMI (kg/m^2)[3]	<30	2	1.6%	1	0.8%
	≥30 and <35	63	50.4%	57	43.8%
	≥35 and ≤40	56	44.8%	70	53.8%
	>40	4	3.2%	2	1.5%
	Mean (SD)	35.20 (3.165)		35.43 (2.650)	
	Median	34.78		35.39	
	Range	29.8, 40.3		29.9, 40.3	
	95% CI	34.640, 35.761		34.967, 35.887	

[1]All characteristics were calculated at the Screening visit

[2]Excess weight at baseline is equal to Baseline weight minus ideal weight based on Met Life

[3]Subjects with BMI <30 and >40 were protocol deviations and excluded from the per protocol population

12.1.4 Effectiveness Results

The study had two co-primary effectiveness endpoints. The first co-primary effectiveness endpoint was mean percent excess weight loss (%EWL) at nine months (3 months after device removal), using the 1983 Metropolitan Life (MetLife) Tables to determine ideal body weight (IBW). The expectation was that subjects in the ORBERA group would, on average, experience at least a 25% EWL. The second co-primary effectiveness endpoint was the percentage of ORBERA-treated subjects with significantly greater weight loss than the control group at nine months (3 months after device removal), where significantly greater weight loss was defined as ≥ 15% EWL over the mean % EWL of the control group. All results presented in this section reflect only those subjects who were randomized to the ORBERA or Control groups (i.e., 125 and 130, respectively).

The result for the first co-primary endpoint was 26.5% EWL (95% CI: 22.9% - 30.2%) based on mITT with LOCF using the MetLife tables to determine IBW; therefore the study did not meet the 95% lower bound confidence interval for the first co-primary endpoint target of 25% EWL. However, the treatment group showed significant Total Body Weight Loss (5.7% TBWL over the control group) at month 9. The study met the second co-primary endpoint of 30% responder rate with 45.6% (95% CI: 36.7%−54.8%), of ORBERA treated subjects achieving at least 15% EWL over the mean of the control group. In terms of percent total body weight loss (TBWL), the ORBERA group achieved a mean of 10.2% TBWL at 6 months (time of device removal), and 9.1% at 9 months (3 months after device removal).

The ORBERA group lost significantly more weight than the control group over the course of the study and was able to maintain significant weight loss through Month 12, six months after removal of the device. Table 8 shows weight loss at key timepoints using measures recommended by the May, 2012 FDA Advisory Panel: %EWL with ideal weight defined using a BMI of 25, %EWL with ideal weight defined by the 1983 Metropolitan Life tables, and %TBWL (mITT with LOCF). Table 9 shows responder rates at these same timepoints with responders defined as achieving at least 5%, 7%, and 10% TBWL (mITT with LOCF).

Table 8: Weight Loss at Key Timepoints using %EWL and %TBWL (mITT with LOCF)

Weight Loss Measure	Group[a]	Month 6		Month 9		Month 12	
		Mean (SD) Range	P-value[b]	Mean (SD) Range	P-value[b]	Mean (SD) Range	P-value[b]
%EWL (based on BMI of 25)	ORBERA	38.4 (27.61) -28.9 - 133.3	<0.001	34.6 (28.4) -42.1 – 138.3	<0.001	29.0 (30.70) -43.2 – 150.1	<0.001
	Control	12.1 (18.58) -20.4 – 68.8		12.3 (19.33) -19.8 – 66.9		11.1 (20.67) -25.6 – 66.7	
%EWL (based on MetLife)	ORBERA	29.6 (20.18) -23.4 – 85.9	<0.001	26.5 (20.70) -34.2 – 86.3	<0.001	22.1 (22.47) -35.0 – 93.7	<0.001
	Control	9.5 (14.4) -15.8 – 56.3		9.7 (15.11) -16.1 – 54.7		8.7 (16.43) -20.6 – 55.0	
%TBWL	ORBERA	-10.2 (6.56) -29.2 – 9.6	<0.001	-9.1 (6.86) -28.0 – 14.0	<0.001	-7.6 (7.48) -32.3 – 14.3	<0.001
	Control	-3.3 (5.02) -19.0 - -5.4		-3.4 (5.33) -19.8 – 5.7		-3.1 (5.90) -22.1 – 8.6	
Weight Loss (lbs)	ORBERA	-21.8 (14.56) -69.0 – 22.2	<0.001	-19.4 (15.56) -82.7 – 32.4	<0.001	-16.2 (17.05) -95.3 – 33.2	<0.001
	Control	-7.0 (10.63) -36.0 – 10.9		-7.1 (1.32) -42.4 – 13.6		-6.3 (12.48) -47.4 – 20.7	

[a]All randomized subjects were used in these analyses, 125 Orbera and 130 Control subjects.
[b]P-values represent treatment group comparisons calculated using a mixed effects model using treatment group, study week, and the respective interaction term assuming random intercepts.

Table 9: Responder rates at Key Timepoints based on 5%, 7%, and 10% TBWL (mITT with LOCF)

Weight Loss Measure	Group	Month 6		Month 9		Month 12	
		Responder rate n (%)	P-value[a]	Responder rate n (%)	P-value[a]	Responder rate n (%)	P-value[a]
5% TBWL	ORBERA	99 (79.2)	<0.001	90 (72.0)	<0.001	75 (60.0)	<0.001
	Control	41 (31.5)		43 (33.1)		39 (30.0)	
7% TBWL	ORBERA	87 (69.6)	<0.001	73 (58.4)	<0.001	54 (43.2)	0.003
	Control	29 (22.3)		34 (26.2)		33 (25.4)	
10% TBWL	ORBERA	58 (46.4)	<0.001	51 (40.8)	<0.001	40 (32.0)	0.003
	Control	15 (11.5)		18 (13.9)		21 (16.2)	

[a]All randomized subjects were used in these analyses, 125 Orbera and 130 Control subjects.
[b]P-values represent treatment group comparisons calculated using a chi-square test.

Some weight regain was seen in the ORBERA group after device removal; however, much of the initial weight loss was maintained through Month 12 (six months after device removal) and the ORBERA group maintained a greater %TBWL than the control group throughout the course of the study. A detailed comparison of the ORBERA, Control, and Run-in groups can be seen Table 10.

Table 10: Observed %TBWL by Treatment Group and Study Week (mITT with LOCF)

Study Week	ORBERA %TBWL	95% CI	Control %TBWL	95% CI
Day 0	0.9%	0.7−1.2	0%	-0.2−0.2
Week 1	3.5%	3.1−3.8	0.9%	0.5−1.2
Week 2	4.1%	3.8−4.5	1.4%	1.1−1.8
Week 4	5.5%	5.1−6.0	2.1%	1.5−2.7
Week 8	7.0%	6.4−7.6	2.6%	2.1−3.2
Week 12	7.9%	7.2−8.7	3.1%	2.5−3.8
Week 16	8.4%	7.5−9.3	3.3%	2.5−4.0
Week 20	8.8%	7.8−9.8	3.4%	2.6−4.2
Week 24	9.1%	8.1−10.2	3.3%	2.5−4.2
Week 26	10.2%	9.0−11.4	3.3%	2.4−4.2
Week 39	9.1%	7.9−10.3	3.4%	2.4−4.3
Week 52	7.6%	6.2−8.9	3.1%	2.0−4.1

Both groups saw decreases in the severity of their comorbid conditions from baseline to Month 9 (Week 39), although only hypertension significantly decreased. However, both groups experienced a comparable improvement of hypertension, indicating that the observed improvement in subjects' comorbid conditions was likely to be attributable to a factor shared by both groups, such as the diet and weight reduction program. A summary of the percent of subjects with the most severe grade(s) of each comorbid condition (diabetes, hypertension, and dyslipidemia) is provided in Table 11.

Table 11: Changes in Comorbid Conditions (mITT with LOCF population)

Comorbid Condition	Treatment Group	Baseline n (%)	Month 6		Month 9		Month 12	
			n (%)	P-value[1]	n (%)	P-value[1]	n (%)	P-value[1]
Type 2 Diabetes (Grade 3)	ORBERA	9 (7.2)	3 (2.4)	0.741	5 (4.0)	0.438	3 (2.4)	0.508
	Control	8 (6.1)	4 (3.1)		3 (2.3)		5 (3.9)	
Hypertension (Grades 3 and 4)	ORBERA	33 (26.4)	22 (17.6)	0.410	14 (11.2)	0.326	11 (8.8)	0.076
	Control	37 (28.5)	18 (13.9)		20 (15.4)		21 (16.2)	
Dyslipidemia (Grades 3 and 4)	ORBERA	49 (39.2)	32 (25.6)	0.286	29 (23.2)	0.639	29 (23.2)	0.438
	Control	39 (30.0)	26 (20.0)		27 (20.8)		25 (19.2)	

[a]All randomized subjects were used in these analyses, 125 Orbera and 130 Control subjects.
[b]P-values represent treatment group comparisons calculated using a chi-square test.

Both study groups also saw improvements in quality of life. Quality of life was measured using the SF-36 health survey and the Impact of Weight on Quality of Life-Lite (IWQOL-Lite).

The SF-36 evaluates 8 domains, and scores range from 0 (poorest health status) to 100 (best health status). The ORBERA group had a significant improvement in all domains of the SF-36 compared to their baseline values, with scores at Month 9 significantly better than the general U.S. population. The ORBERA group had a larger effect size compared to the control group in all domains of the SF-36 at Month 9. SF-36 mean scores for the ORBERA and control group are provided in Table 12.

Table 12: SF-36 Health Survey Mean Scores at Baseline and Month 9 by Study Group (mITT with LOCF)

Category	ORBERA (N=123)[a]			Control (N=130)[a]			
	Baseline Mean (SD)	Month 9 Mean (SD)	Effect Size[b]	Baseline Mean (SD)	Month 9 Mean (SD)	Effect Size[b]	P-value[c]
Physical Function	71.4 (22.09)	86.2 (18.62)	0.67	73.7 (21.14)	81.4 (18.74)	0.36	0.002
Role Physical	78.5 (21.59)	89.9 (17.44)	0.53	80.3 (23.07)	83.2 (22.60)	0.13	<0.001
Bodily Pain	72.8 (21.88)	82.4 (21.27)	0.44	75.4 (22.34)	75.3 (24.11)	0.00	<0.001
General Health	61.9 (20.22)	76.0 (18.04)	0.70	63.4 (20.11)	65.3 (21.48)	0.09	<0.001
Vitality	52.7 (18.19)	64.0 (19.77)	0.62	53.0 (19.11)	56.0 (20.87)	0.16	<0.001
Social Function	80.5 (21.89)	89.6 (17.94)	0.42	80.8 (23.30)	81.3 (23.36)	0.02	0.001
Role Emotional	84.0 (22.65)	89.7 (17.56)	0.25	84.6 (20.81)	85.3 (20.54)	0.03	0.050
Mental Health	74.0 (17.91)	78.2 (16.44)	0.23	73.7 (16.59)	72.2 (17.66)	-0.09	0.007

[a]All randomized subjects with non-missing baseline values were used in these analyses, 123 ORBERA™ and 130 Control subjects.
[b]Effect size is the ratio of the difference between the baseline mean and Month 9 visit to the baseline standard deviation.
[c]P-values represent treatment group comparisons calculated using an ANOVA model.

The IWQOL-Lite consists of 31 scale items to assess obesity-related quality of life. The ideal scores (where 0 is worst and 100 is best) for the ORBERA and Control groups are summarized in Table 13. Significant improvement from baseline was observed for both groups, but the effect sizes for the ORBERA-group were greater than the effect sizes for the Control group.

Table 13: Impact of Weight on Quality of Life-Lite (IWQOL-Lite) Total Scores at Baseline and 6, 9, and 12 Months (mITT with LOCF population)

Timepoint	ORBERA[a] (N=121)		Control[a] (N=127)		
	Mean Score	Effect Size[b]	Mean Score	Effect Size[b]	P-value[c]
Baseline	68.4	NA	68.5	NA	NA
Month 6	80.7	0.66	73.2	0.27	<0.001
Month 9	82.5	0.75	75.3	0.39	<0.001
Month 12	83.0	0.78	76.6	0.47	0.001

[a]All randomized subjects with non-missing baseline values were used in these analyses, 121 Orbera and 127 Control subjects.
[b]Effect size is the ratio of the difference between the baseline mean and each follow-up visit to the baseline standard deviation.
[c]P-values represent treatment group comparisons calculated using an ANOVA model.

12.2 ORBERA US Post Approval Study (OPAS-1)

12.2.1 Study Objective

The objective of this study was to provide additional safety and effectiveness data on Orbera. It was required as a condition of FDA approval.

12.2.2 Study Design

The ORBERA Post-Approval Study, known as OPAS-1, was a prospective, multicenter, open-label, post-approval study of the safety and effectiveness of ORBERA as an adjunct to weight reduction for obese adults. Study subjects participated in a 12-month behavioral modification program (i.e., 6 months with ORBERA in place plus 6 months after ORBERA was removed). All subjects had routine visits throughout the study to evaluate safety and effectiveness, with a total of 26 scheduled visits over the 1-year period.

12.2.3 Study Population

The study population include patients 22 years and older, with BMI scores between 30-40 kg/m2, who had failed to respond to traditional lifestyle modification.

12.2.4 Data Source

The data associated with this study encompasses information obtained from the date of FDA approval for the study (February 26, 2016) through the completion of the study, which was accepted by FDA on April 7, 2020. IRB approval was obtained by all sites prior to initiation and training for the study. Prior to data lock, all queries were closed and the principal investigators signed off on the completed CRFs for their sites.

12.2.5 Key Study Endpoints

The primary endpoint associated with this study was to demonstrate that the incidence of device and procedure-related Serious Adverse Events (SAEs) after 26 weeks of ORBERA treatment is no greater than 15%.

The key secondary study objective was to demonstrate that the mean percent Total Body Weight Loss (%TBWL) was greater than 7.5% at ORBERA® treatment conclusion (study week 26).

12.2.6 Total Number of Enrolled Study Sites and Subjects, Follow-up Rate

Eleven (11) sites enrolled a total of 284 subjects. Of these subjects:

- 18 were not eligible at the baseline visit following informed consent and
- 8 subjects were not eligible at the time of balloon placement,

The treatment group was made up of the remaining 258 subjects, 234 (90.7%) of which completed the study. The remaining 24 treated subjects were discontinued from the study before the conclusion of their expected protocol follow-up. Key demographics and baseline characteristics are presented in Table 14 and subject follow-up rates are summarized in Table 15.

Table 14: Subject Demographics and Baseline Characteristics

Demographics for Enrolled Populations	Category	Baseline (n = 284)	
		n	(%)
Gender	Female	245	86.3%
	Male	39	13.7%
Age (years)	24-29	18	6.3%
	30-39	57	6.3%
	40-49	95	20.1%
	50-59	80	33.5%
	60 & over	34	28.2%
	Mean (SD)	46.6 (10.6)	
	Median	46.8	
	Range	23.9 – 72.7	
	95% CI	[45.4, 47.8]	
Race	Caucasian	217	76.4%
	Black (not of Hispanic origin)	32	11.3%
	Hispanic	20	7.0%
	Other	12	4.2%
	Asian	3	1.1%
Excess Weight[2] (lbs.)	Mean (SD)	62.0 (20.3)	
	Median	57.6	
	Range	26.0 - 118.6	
	95% CI	[59.6, 64.4]	
BMI (kg/m^2)[3]	<30	0	N/A
	≥30 and <35	147	51.8%
	≥35 and ≤40	137	48.2%
	>40	0	N/A
	Mean (SD)	35.1 (2.9)	
	Median	34.8	
	Range	30.0, 40.0	
	95% CI	[34.8, 35.4]	

Table 15: Subject Accountability by Milestone Visit

	Baseline	Placement	Removal	Study Exit
Theoretical[1]	284	266	258	258
Ineligible After Enrollment	18	8	0	0
Deaths (cumulative)	0	0	0	0
Withdrew consent (cumulative)[2]	0	0	0	2
Early Study Exit (cumulative)[3]	NA	0	0	NA
Early Removal / LTF (cumulative)[4]	0	0	0	4
Expected[5]	266	258	258	252
Per Protocol Visit	265	258	239	233
Any Data Visit	266	258	257	245
% Follow-up - Per Protocol	99.6%	100%	92.6%	92.5%
% Follow-up - Any Data	100%	100%	99.6%	97.2%

[1] Theoretical is the number of subjects available for that study visit (baseline=number enrolled, placement=expected from baseline, all other study visits=number expected from placement)
[2] Subjects that withdrew consent and did not complete an early exit visit
[3] Subjects that completed the Exit visit early (all early exits were after balloon removal)
[4] Subjects with an early removal (considered a study failure) that did not complete the study follow-up
[5] Expected = theoretical – ineligible after enrollment – deaths – withdrew consent – early study exit – early removal

12.2.7 Study Visits and Length of Follow-Up

Study visits were conducted at baseline, treatment, and then 1, 2 and 4 weeks following balloon placement, then every four weeks until week 48, followed by a final visit at week 52. Adverse events and weight loss were recorded at all follow-up visits.

12.2.8 Final Safety Findings

Through the course of the study, no unanticipated adverse device effects or any deaths were reported. The incidence of device related SAEs was 8.9% (23/257), with an upper limit of 1-sided 95% confidence interval 12.4% (p-value = 0.003), thus the endpoint was met.

Table 16 summarizes the primary endpoint analysis and imputations associated with the study. Both imputations for SAE incidence also satisfied the endpoint. Finally, a tipping point analysis was performed to identify the incidence rate of SAEs that would not satisfy the endpoint criteria for the study, which was 11.6%. Thus, seven additional cases would be necessary to tip the analysis to non-significant. Table 17 summarizes the SAEs that were observed.

Table 16: Primary Endpoint Summary, Full Analysis Population

Analysis	Criteria	SAE Incidence Rate	Upper Limit of 1-sided 95% CI, p-value
Completers[1]	≤ 15%	23 / 257 (8.9%)	12.4%, p = 0.0033
Imputation (Best Case)		23 / 258 (8.9%)	12.4%, p = 0.0031
Imputation (Worst Case)		24 / 258 (9.3%)	12.8%, p = 0.052
Tipping Point		30 / 258 (11.6%)	15.4%, p = 0.065

Table 17: All Device Related Serious[1] Adverse Events in OPAS-1

Device-Related Serious Adverse Event	Number of subjects out of 258 (% of subjects)	Number of Events	Onset (days to event)	Number of subjects with event that had device removed (% of subjects with device removal)
Device intolerance[2]	13 (5%)	28	**Mean:** 24 **Median:** 9 **Range:** 1 - 125	12/13 (92.3%)
Device Intolerance due to Hyperinflation	4 (1.6%)	4	**Mean:** 72 **Median:** 57 **Range:** 10 - 166	4/4 (100%)
Impaired Gastric Emptying	2 (0.8%)	2	**Mean:** 38 **Median:** 33 **Range:** 1 - 87	2/2 (100%)
Hypokalemia	1 (0.4%)	1	98	1/1 (100%)
Diarrhea	1 (0.4%)	1	18	1/1 (100%)
Bloating	1 (0.4%)	1	63	1/1 (100%)
Hyperinflation[3]	1 (0.4%)	1	74	1/1 (100%)

1 A serious adverse event is one that:
- Led to death,
- Led to a serious deterioration in the health of a patient that:
- Resulted in a life-threatening illness or injury,
- Resulted in a permanent impairment of a body function or body structure,
- Required in-patient hospitalization or prolonged hospitalization,
- Resulted in medical or surgical intervention to prevent permanent impairment to a body function or body structure,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

2 Device Intolerance is defined as severe and intolerable symptoms of gastrointestinal upset (i.e., nausea, vomiting, reflux, pain/epigastric discomfort)

3 Though this instance of Hyperinflation was coincided with a report of abdominal pain (i.e. Device Intolerance due to Hyperinflation) it was counted as a separate SAE.

Forty-seven subjects (47/258 or 18.2%) had an early removal; thirty-two of these subjects had the early removal for an adverse event / gastrointestinal intolerance, device malfunction or dissatisfaction with the treatment (32/258 or 12.4%).

There were no serious adverse events reported that were related to the endoscopic procedure itself.

[1] The Completers Population is defined as those subjects that completed the 26-week treatment period with the balloon.

12.2.9 Final Effectiveness Findings

The key effectiveness endpoint was to demonstrate that the treatment response (i.e. mean percent Total Body Weight Loss (%TBWL)) was greater than 7.5% at the time of ORBERA treatment conclusion (26 weeks).

- %TBWL was derived at each post-placement study visit for each subject where a weight measurement is collected.
- Subjects were categorized as a responder at each visit if they achieved at least 7.5%TBWL, programmatically this would be any %TBWL value being ≤ -7.5%.

While weight loss was demonstrated as early as 2 weeks post-implantation, maximum weight loss was achieved at the time of removal (average %TBWL = -12.5%). In fact, the 95% confidence interval confirmed at least -7.5% TBWL from 12 weeks through 48 weeks following placement. Furthermore, an estimated mean %TBWL of -12.5% (with a lower 95% confidence interval of -11.8) after 26 weeks of treatment was achieved (compared to estimated mean %TBWL of -10.3% observed in the pivotal study), thus the criteria for success was met and the efficacy of the device was confirmed to perform as well as in the pivotal study.

The trends observed in the confidence interval were similar to the percent of treatment responders. Over half the population were defined as responders to the treatment by 8 weeks which increased to over three fourths of the population being a responder at the time of removal. While weight was regained after removal, over half of the subjects continued to be a responder through the 48-week visit. Table 18 summarizes these results.

Table 18: Summary of Percent Total Body Weight Loss (%TBWL) and Responders by Study Visit, Efficacy Population

Study Visit	# of Patients	Responders	Mean (SD)	Median	Min, Max	LS Mean, 95% CI
Week 1	254	3 / 254 (1.2%)	-3.6 (1.66)	-3.6	-10.7, 0.8	-3.6 (-4.3, -2.9)
Week 2	252	22 / 252 (8.7%)	-4.6 (1.97)	-4.4	-12.4, -0.4	-4.6 (-5.3, -3.8)
Week 4	249	59 / 249 (23.7%)	-6.1 (2.04)	-6.1	-12.2, 1.9	-6.1 (-6.8, -5.4)
Week 8	250	136 / 250 (54.4%)	-7.9 (3.07)	-8.0	-17.4, 0.1	-7.9 (-8.6, -7.2)
Week 12	248	160 / 248 (64.5%)	-9.2 (3.93)	-9.2	-21.2, 0.8	-9.2 (-9.9, -8.5)
Week 16	246	174 / 246 (70.7%)	-10.2 (4.64)	-10.0	-24.8, 0.9	-10.2 (-10.9, -9.5)
Week 20	242	169 / 242 (69.98%)	-10.6 (5.45)	-10.4	-26.2, 2.7	-10.6 (-11.4, -9.9)
Week 24	245	170 / 245 (69.4%)	-10.9 (6.00)	-10.6	-28.3, 2.4	-10.9 (-11.6, -10.2)
Week 26	251	193 / 251 (76.9%)	-12.45 (6.27)	-11.8	-33.5, 1.9	-12.5 (-13.2, -11.8)
Week 28	243	169 / 243 (69.5%)	-11.5 (6.63)	-11.1	-39.4, 2.9	-11.5 (-12.2, -10.8)
Week 32	238	151 / 238 (63.4%)	-10.6 (6.84)	-10.1	-30.3, 4.2	-10.6 (-11.3, -9.8)
Week 36	235	146 / 235 (62.1%)	-10.1 (7.11)	-9.8	-32.8, 5.7	-10.1 (-10.8, -9.4)
Week 40	233	133 / 233 (57.1%)	-9.5 (7.29)	-9.1	-33.4, 5.9	-9.5 (-10.2, -8.8)
Week 44	234	130 / 234 (55.6%)	-9.1 (7.42)	-8.4	-33.2, 7.0	-9.1 (-9.9, -8.4)
Week 48	231	122 / 231 (52.8%)	-8.6 (7.50)	-8.1	-31.4, 8.2	-8.6 (-9.3, -7.8)

Study Visit	# of Patients	Responders	Mean (SD)	Median	Min, Max	LS Mean, 95% CI
Week 52	240	115 / 240 (47.9%)	-8.0 (7.74)	-7.0	-32.9, 8.6	-8.0 (-8.7, -7.3)

Table 19 summarizes the %TBWL at the completion of treatment for all analysis populations and imputed data. The "Completers Population" is defined as those subjects that completed the 26-week treatment period with the balloon. The p-value value for all populations was <0.0001, thus the weight loss from this study satisfied the success criteria. Power analysis of the completers population demonstrated that the power remained > 99% despite the lower sample size from estimate (210 versus 230).

Table 19: Secondary Efficacy Endpoint (%TBWL[1]): All Analysis Populations.

Analysis Population	# of subjects	Responders[2]	Mean (SD)	Median	Min, Max	LS Mean [3] (95% CI)
Completers Population	210	164 / 210 (78.1%)	-12.6 (6.10)	-12.0	-33.5, 0.6	-12.6 (-13.4, -11.8)
Efficacy Population[3]	251	193 / 251 (76.9%)	-12.5 (6.27)	-11.8	-33.5, 1.9	-12.5 (-13.2, -11.8)
Full Analysis Population[4]	255	195 / 255 (76.5%)	-12.4 (6.26)	-11.7	-33.5, 1.9	-12.4 (-13.1, -11.74)
Imputation[5]	258	196 / 258 (76.0%)	-12.5 (6.27)	-11.8	-33.5, 1.9	-12.5 (-13.1, -11.8)

1 %TBWL = 100 x (weight of post-placement visit – baseline weight) / baseline weight. Negative %TBWL value indicates weight loss.
2 Subjects were reported as responders if they achieved at least 7.5%TBWL
3 Least-square mean and associated 95% confidence interval from mixed effects model adjusting for visit with subject as random effect
4 All subjects that completed visit are reported, including those that had an early removal
5 MI=Multiple Imputation; fully conditional specification (FCS) methods used for %TBW; multiple imputations were built using age, gender, race and weight as potential risk factors

For the efficacy population, weight loss parameters (Percent Excess Weight Loss (%EWL) and change in Body Mass Index) are summarized in Table 20 by study visit. Subjects demonstrated weight loss immediately following treatment with an estimated mean %EWL of 13.6 as early as 1 week following placement. Excess weight loss continued progressively at each study visit until reaching maximum estimated mean %EWL (46.9) at the time of removal.

Though gradual weight gain was observed in subjects following balloon removal (as demonstrated by decreased estimated mean %EWL), at all post removal follow-up visits the estimated mean %EWL remained above 30 with 44.2% of the subjects (106/240) demonstrating a %EWL of at least 30 by the final study visit. This suggests that at 6 months following balloon removal subjects were able to maintain successful weight loss. Additionally, this data demonstrates that:

- the trends observed with %EWL are similar to those observed with respect to %TBWL
- at all visits, subjects achieved a decrease in BMI from baseline
- the maximum difference in BMI was realized at the time of removal (-4.3 estimated mean);
- the BMI change at 52 weeks was similar to that attained by the 8-week visit (-2.8 estimated mean).

Table 20: Summary of Percent Loss Parameters by Study Visit, Efficacy Population

Week	# of subjects	% Excess Weight Loss (%EWL)[1]				Change in Body Mass Index (BMI) from Baseline[2]			
		Mean (SD)	Median	Min, Max	LS Mean, 95% CI[3]	Mean (SD)	Median	Min, Max	LS Mean, 95% CI[3]
1	254	13.6 (7.35)	12.6	-2.6, 52.1	13.6 (10.6, 16.6)	-1.3 (0.58)	-1.3	-3.4, 0.3	-1.3 (-1.5, -1.0)
2	252	16.9 (8.6)	15.0	1.1, 47.0	16.9 (14.0, 19.9)	-1.6 (0.69)	-1.6	-4.2, -0.1	-1.6 (-1.8, -1.4)
4	249	22.6 (9.78)	20.9	-7.5, 57.8	22.6 (19.7, 25.6)	-2.1 (0.71)	-2.1	-3.9, 0.6	-2.1 (-2.4, -1.9)
8	250	29.3 (13.85)	27.8	-0.5, 80.3	29.3 (26.3, 32.3)	-2.8 (1.07)	-2.8	-6.3, 0.0	-2.8 (-3.0, -2.5)
12	248	34.4 (17.2)	31.3	-2.3, 111.2	34.4 (31.4, 37.4)	-3.2 (1.38)	-3.2	-7.5, 0.3	-3.2 (-3.5, -3.0)
16	246	38.1 (20.47)	35.2	2.9, 125.1	38.1 (35.1, 41.1)	-3.6 (1.6)	-3.5	--8.8, -0.3	-3.6 (-3.8, -3.3)
20	242	39.9 (23.68)	35.4	-7.5, 145.2	39.9 (36.9, 43.0)	-3.7 (1.88)	-3.7	-9.2, 1.0	-3.7 (-4.0, -3.5)
24	245	40.9 (25.6)	35.8	-6.8, 157.6	40.9 (37.9, 43.9)	-3.8 (2.07)	-3.7	-9.9, 0.9	-3.8 (-4.0, -3.5)
26	251	46.9 (27.58)	41.2	-7.5, 173.7	46.9 (43.9, 49.9)	-4.3 (2.15)	-4.2	-11.7, 0.6	-4.3 (-4.6, -4.1)
28	243	43.6 (30.01)	37.1	-9.8, 229.7	43.76 (40.6, 46.7)	-4 (2.25)	-3.9	-11.9, 1.0	-4.0 (-4.2, -3.8)
32	238	40 (28.85)	35.1	-11.9, 174.9	40.0 (37.0, 43.1)	-3.7 (2.35)	-3.6	-11.2, 1.7	-3.7 (-3.9, -3.4)
36	235	38.4 (29.8)	33.2	-15.5, 174.3	38.4 (35.3, 41.4)	-3.5 (2.45)	-3.4	-12.2, 2.3	-3.5 (-3.8, -3.3)
40	233	36.1 (30.06)	31.5	-16.1, 182.3	36.1 (33.0, 39.2)	-3.3 (2.53)	-3.1	-12.4, 2.3	-3.3 (-3.6, -3.1)
44	234	34.8 (30.26)	30.8	-19.3, 169.6	34.8 (31.7, 37.9)	-3.2 (/ 2.57)	-2.9	-12.3, 2.7	-3.2 (-3.4, -2.9)
48	231	32.8 (30.44)	27.8	-22.7, 167.5	32.8 (29.7, 35.9)	-3 (2.6)	-2.8	-11.6, 3.2	-3.0 (-3.2, -2.7)
52	240	30.6 (30.77)	25.4	-26.5, 166.9	30.6 (27.5, 33.6)	-2.8 (2.71)	-2.5	-12.2, 3.4	-2.8 (-3.0, -2.5)

[1] %EWL = 100 (weight of post-placement visit – baseline weight) / excess weight. Positive %EWL indicates weight loss; where excess weight = baseline weight – ideal weight and ideal weight = 25 / 703 * (height)^2

[2] Change in BMI = (BMI of post-placement visit – baseline BMI) / Baseline BMI. Negative change indicates weight loss

[3] Least-square mean and associate 95% confidence interval from mixed effects model adjusting for visit with subject as random effect

12.2.10 Study Strengths and Weaknesses

The strengths of this study include that it was sufficiently powered to meet the primary safety endpoint and provided corroborating evidence to support effectiveness. The follow-up rate was over 90% over the course of 52 weeks. The weaknesses include that the study was not powered to make a statistical determination on the rate of very rare events (e.g. death and pancreatitis). Also, the study was not designed a priori to evaluate the presence of microbes contained within balloons inflating after placement.

12.3 Global Product Experience and Clinical Studies

ORBERA has been approved in many countries since the 1990's. As of March 30, 2020 more than 300,000 devices have been distributed to countries with ORBERA™ approval. No regulatory approvals have been revoked or withdrawn. The Apollo complaint database houses vigilance reports for adverse events submitted to various competent authorities by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters such as healthcare professionals, patients, and consumers. Device- and procedure-related adverse events or complaints reported through clinical product surveillance and literature reviews are contained within this data. A total of 10,212 complaints (i.e. individual events) spanning a period from January 1, 2008 to March 30, 2020 are presented in Table 21; however, this data has not been scientifically validated and may include duplication of some events due to multiple sources of data collection. Some events have not been directly attributed to ORBERA. Duration of device support and clinical course are unknown; therefore events such as device deflation (i.e. collapse) may be related to use longer than a period of 6 months.

Table 21: ORBERA device- and procedure- related adverse events and complaints reported through clinical product surveillance[1] between January 1, 2008 and March 30, 2020

Events	Count[1]	Rate[2]
Premature or Partial Detachment of Fill-Tube	1666	0.988%
Vomiting	1019	0.605%
Device Deflation	924	0.548%
Pain	885	0.525%
Early Removal	678	0.402%
Nausea	658	0.390%
Difficulty Adding Saline	641	0.380%
Other[3]	607	0.360%
Spontaneous hyperinflation	326	0.193%
Reflux	264	0.157%
Intolerance	225	0.133%
Unsuccessful placement	221	0.131%
Malaise	216	0.128%
Dehydration	194	0.115%
Irritation/inflammation	174	0.103%
Unsatisfactory weight loss	147	0.087%
Obstruction • Intestinal Obstruction: 23 (0.014%) • Stomach Obstruction: 86 (0.051%) • Unspecified Obstruction: 27 (0.016%)	136	0.081%
Premature Fill-Tube Detachment (Out of Box)	99	0.059%
Balloon Leak (Reported During Placement)	76	0.045%
Gas	72	0.043%
Cramping	67	0.040%
Removal Tool Failure	67	0.040%
Abdominal Distension	60	0.036%
Bloating	60	0.036%
Constipation	57	0.034%
Stomach Perforation	53	0.031%

Events	Count[1]	Rate[2]
Ulcer	50	0.030%
Diarrhea	49	0.029%
Device displacement or migration	43	0.026%
Eructate	42	0.025%
Delayed Gastric Emptying	36	0.021%
Abnormal Blood Level[4]	36	0.021%
Lack of Satiety	33	0.020%
Death	31	0.018%
Infection	29	0.017%
Indigestion	28	0.017%
Pancreatitis	26	0.015%
Dysphagia	22	0.013%
Device visibility or palpability	21	0.012%
Difficulty Removing Balloon	21	0.012%
Aspiration or Aspiration Pneumonia	20	0.012%
Hematemesis or hematochezia	19	0.011%
Gastroparesis	17	0.010%
Erosion	17	0.010%
Necrosis	16	0.009%
Cardiac Complication	13	0.008%
Dyspnea	13	0.008%
Esophageal perforation	10	0.006%
Ischemia	10	0.006%
Respiratory Disorder	9	0.005%
Hernia	5	0.003%
Pulmonary Embolism	4	0.002%
Total	10,212	6.058%
Balloons sold worldwide from January 1, 2008 through March 30, 2020	168,569	

1. Some complaints were counted in multiple categories due to multiple events being reported in one complaint. The above numbers do not indicate number of devices nor patients involved. Includes complaints reported against unknown catalogs. Does not include non-device related events.
2. The event rate represents the counts of an event divided by the number of devices distributed as of the reporting cut-off on March 30, 2020. Note that the number of devices distributed may be greater than the number of devices placed.
3. Includes infrequently occurring events such (i.e. ≤ 0.010%) as Hiccups, Dizziness, Fever, Halitosis, Muscle Spasms, Flatulence, Retching, Hair Loss, Peritonitis, Fainting, etc.
4. Category includes increased or decreased blood levels of substances such as Potassium, Lipase, Creatine, blood urea nitrogen (BUN) levels or Sodium (hypernatremia), etc.

Two sponsor-initiated clinical trials were conducted outside of the U.S., one in one in Australia (n=74, 37 treatment and 37 control subjects), described in section 11.3.1, and one in France (n=36 treatment subjects), described in section 11.3.2. The adverse event profile for these two studies were similar to the adverse event profile seen in the U.S. pivotal study. There were no deaths and no unanticipated adverse device effects in either study.

12.3.1 ORBERA Australian Study

The ORBERA Australian study was a randomized, open-label, controlled study conducted at a single center in Australia. Male and female subjects between 18 and 60 years of age with a BMI between 30 and 40 kg/m^2 for at least 2 years and who had metabolic syndrome with at least one obesity-related comorbidity were enrolled. Subjects randomized to treatment had ORBERA in place for the first 6 months of the study, with all subjects participating in a 12-month behavioral modification program of diet and exercise. A total of 74 subjects were randomized, with 37 subjects in each arm. Thirty-one subjects (31) underwent ORBERA placement. Fifty-nine (59) subjects completed the first 6 months of the study, 29 in the ORBERA group and 30 in the control group, and 55 completed the full 12-month study, 23 in the ORBERA group and 22 in the control group.

Safety events were as expected for the ORBERA group, with the majority of the ORBERA group reporting gastrointestinal adverse events during the first two weeks after placement. The most common device-related adverse events were nausea and vomiting (74.2%), abdominal pain (54.8%), gastroesophageal reflux (38.7%), lethargy (32.3%), and dehydration (25.8%). These events typically resolved within two weeks. Two subjects experienced 7 serious adverse events which led to removal prior to 6 months. Serious adverse events included: gastroesophageal reflux, vomiting, nausea, and abdominal pain. There were no deaths or unanticipated adverse device effects.

12.3.2 French ORBERA Study

The French ORBERA study was a prospective, open-label, single-center post-marketing study. Forty male and female subjects between 18 and 60 years of age with BMI 30 to 35 kg/m2 with at least one obesity-related comorbidity, or BMI 35 to 40 kg/m2 with or without a comorbidity were enrolled. Thirty-six subjects underwent ORBERA placement in this 48-week study. The first 24 weeks included ORBERA placement in conjunction with a medically supervised diet. After a maximum of 180 days, ORBERA was removed. Subjects continued the diet for an additional 24 weeks. The study consisted of a screening visit, ORBERA placement, follow-up visits at Weeks 1, 4, and 12, ORBERA removal at Week 24, and two additional follow-up visits at Week 36 and 48.

The most common device-related adverse events experienced by this study population were nausea (27.9%), vomiting (19.7%), esophagitis (14.8%), and upper abdominal pain (11.5%). Most device-related adverse events lasted less than a month and resolved without sequelae. Three serious adverse events occurred in two subjects which led to removal prior to 6 months. Serious adverse events included vomiting and asthenia, ionic disorder, and vomiting with dehydration.

13 HOW SUPPLIED

Each IGB System contains an IGB positioned within a “Placement Catheter Assembly” and a “Fill Kit”. All are supplied NONSTERILE and FOR SINGLE USE ONLY. All components should be handled carefully.

Materials Included:

- One (1) Intragastric Balloon (IGB) System consisting of:
    - One (1) Placement Catheter Assembly (i.e. Sheath Assembly) containing the IGB
    - One (1) Fill Kit with IV Spike

Materials Not Included:

- Endoscope
- Surgical Gel
- Sterile Saline
- Sterile 50cc Syringe
- Removal tools (i.e. sheathed needle catheter, long jaw or wire prong grasper)

13.1 Cleaning Instructions

In the event that the product becomes contaminated prior to use, it should not be used but should be returned to the manufacturer.

CAUTION: DO NOT SOAK THE PRODUCT IN A DISINFECTANT because the silicone elastomer may absorb some of the solution, which could subsequently leach out and cause a tissue reaction.

13.2 Disposal

Dispose of any used or explanted device’s or device components in accordance with any local regulations for medical waste.

14 Directions For Use

The IGB is supplied positioned within the Placement Catheter Assembly. Inspect the package seal and the Placement Catheter Assembly for damage prior to use. It should not be used if any damage is noted. A back-up IGB should be available at the time of placement.

DO NOT REMOVE THE IGB FROM THE PLACEMENT CATHETER ASSEMBLY.

A Fill Kit is provided to assist with the IGB deployment.

CAUTION: If the IGB becomes separated from the catheter or sheath prior to placement, do not attempt to use the IGB or reinsert the IGB into the sheath.

14.1 IGB Placement and Filling

Prepare the patient for endoscopy. Inspect the esophagus and stomach endoscopically and then remove the endoscope. If there are no contraindications, insert the Placement Catheter Assembly containing the IGB gently down the esophagus and confirm that it is below the lower esophageal sphincter and well within the stomach cavity before removing the guidewire (if present) and proceeding. The small size of the Placement Catheter Assembly allows ample space for the endoscope to be reinserted for observing the IGB filling steps.

14.2 IGB Filling

Using aseptic technique, place the Fill Kit spike into the sterile saline bag. Attach a sterile syringe to the valve of the Fill Kit and prime it. Connect the Luer-Lock connector on the Placement Catheter to the Fill Kit valve. Proceed to fill the IGB with sterile saline, verifying with the endoscope that the IGB is within the stomach.

CAUTION: Fill the balloon with sterile saline. An aseptic technique, similar to changing IV fluids (e.g. use of clean or sterile gloves, sterile syringe, etc.), is recommended. Though the cause of hyperinflation is unknown, it may be caused by fungal or bacterial microbes contaminating the balloon. One recommended mitigation is to avoid contaminating the saline within the balloon with micro-organisms that may lead to spontaneous hyperinflation.

CAUTION: During the filling process the Placement Catheter must remain slack. If the catheter is under tension during this process, the tip of the catheter may dislodge from the IGB, preventing further IGB deployment.

WARNING: Rapid fill rates will generate high pressure which can damage the IGB valve or cause premature detachment from the tip of the Placement Catheter.

14.3 Filling Recommendations

The expandable design of the IGB permits a fill volume range of 400cc (minimum) to a maximum of 700cc. The IGB should not be under-filled or over-filled with volumes <400cc or >700cc, as under- or over-filling the IGB could cause higher risk for serious side effects, such as migration (under-filled IGB) or gastric rupture/perforation (over-filled IGB). Once filled, the IGB is not adjustable.

To determine the ideal IGB size to produce the greatest weight loss effectiveness, 2 independent reviewers searched PubMed and Embase to identify full-length ORBERA clinical studies. A total of 80 studies with 8,506 patients were included in this meta-analysis of global ORBERA data. Figure 5, meta-regression analysis of IGB fill volume correlation with total body weight loss (TBWL), demonstrates fill volume ranges from 500cc to 700cc. Results at 6 months do not seem to differ with volume ($p=0.24$).[1] Therefore, based on this, the recommendation should be filling volume between 500cc to 650cc; however the pivotal clinical study's safety and effectiveness data for this device was only tested with fill volumes of 550cc ± 50cc.

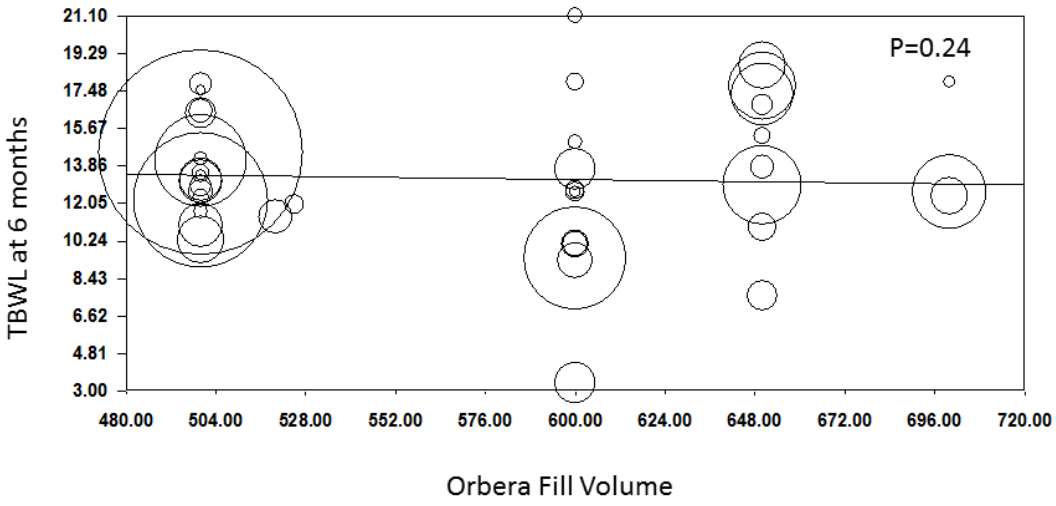

Figure 5: Meta-regression analysis of balloon fill volume correlation with total body weight loss (TBWL). [1]

Note: the size of the circles on the graph corresponds with the study size. Figure courtesy of Dr. Barham Abu-Dayyeh.

The following filling recommendations are provided to avoid inadvertent damage to the valve of the balloon or premature detachment from the placement catheter:

- Always use the IGB Fill Kit provided.
- Always use a sterile 50cc syringe to fill the IGB. Use of smaller syringes can result in very high pressures of 30, 40, and even 50 psi, which can damage the IGB valve.
- With a sterile 50cc syringe, each filling stroke should be done slowly (minimum of 10 seconds) and steadily. Slow, steady filling will avoid the generation of high pressure to the valve.
    - **WARNING:** Rapid fill rates will generate high pressure which can damage the IGB valve or cause premature detachment from the tip of the Placement Catheter.
    - Filling should always be completed under direct visualization (gastroscopy). Integrity of the IGB valve should be confirmed by observing the valve lumen as the Placement Catheter is removed from the valve of the IGB.
    - An IGB with a leaking valve must be removed immediately. A partially filled IGB can result in a bowel obstruction, which can result in death. Bowel obstructions have occurred as a result of unrecognized or untreated IGB deflation (i.e. collapse).

NOTE: Any IGBs that leak should be returned to Apollo Endosurgery, with a completed product return field note describing the event. Your assistance with our continuing quality improvement efforts is appreciated.

A minimum fill volume of 400cc is required for the IGB to deploy completely from the Placement Catheter. After filling the IGB, remove the Fill Kit from the catheter.

When filled, the IGB is released by pulling the Placement Catheter gently while the IGB is against the tip of the endoscope or the lower esophageal sphincter.

Continue to pull the Placement Catheter until it has detached from the IGB's self-sealing valve. Once detached, the placement of the IGB should be visually inspected as well as for the presence of any fluid leaks.

14.4 IGB Placement and Filling (Step-by-Step)

1. Prepare the patient according to hospital protocol for sedation and endoscopy.
2. Perform endoscopic inspection of the esophagus and stomach.
3. Remove endoscope.
4. If there are no contraindications:
    a. Lubricate the sheath of the Placement Catheter assembly with surgical lube-gel.
    b. Gently insert the Placement Catheter into the esophagus and into the stomach.
5. Reinsert the endoscope while the IGB is in situ to observe filling steps. The IGB MUST be below the lower esophageal sphincter and well within the stomach cavity.
6. If present, remove the guidewire from the Placement Catheter.
7. Attach the sterile 50cc syringe to the Luer lock of the Fill Kit's 3-way stopcock and then insert the spike of the Fill Kit into a bag of sterile normal saline solution for injection (.9 NS).
8. Slowly fill the IGB with sterile saline, 50cc at a time. Repeat up to a minimum fill volume of 400cc to a maximum fill volume of 700cc (14 strokes).
9. Gently remove the Placement Catheter and inspect the IGB valve for leakage.

14.5 IGB Removal (Step-by-Step)

1. Ensure that the patient has been on a liquid diet for 72 hours and NPO (i.e. nothing by mouth) for a minimum of 12 hours before attempting removal. Whether this regimen has been followed or not (i.e. in the case of an urgent removal), due to the potential for residual gastric contents in some patients, additional precautions for aspiration should be considered. In higher risk patients with signs and symptoms suggestive of severely delayed gastric emptying and/or gastric outlet obstruction, a focused physical examination for abdominal distension and/or succussion splash should be performed, followed by radiographic evaluation if succussion splash is absent and epigastrium full or tender. If radiographic evaluation is positive for distended stomach with or without an antral IGB, then nasogastric decompression should be considered, the airway should be secured, and general anesthesia employed.
2. Prepare the patient according to hospital protocol for sedation and endoscopy.
   Additionally, consider administering a smooth muscle relaxant such as intravenous glucagon to relax the lower esophageal sphincter.
3. Insert the endoscope into the patient's stomach.

4. Assess for the presence of food. If food is present in the stomach the procedure should be delayed. If emergent removal, the airway should be protected prior to proceeding.
5. Get a clear view of the filled IGB using the endoscope.
6. Insert a sheathed needle catheter down the working channel of the endoscope.
7. Use the advanced exposed needle to puncture the IGB.
8. Push the needle catheter through the IGB shell well into the IGB.
9. Remove the needle from the catheter.
10. Apply suction to the deeply inserted catheter until all fluid is evacuated from the IGB.
11. Remove the catheter from the IGB and out of the working channel of the endoscope.
12. Insert a long jaw or wire prong grasper through the working channel of the endoscope.
13. Grab the IGB with the grasper (ideally at the opposite end of valve if possible).
14. With a firm grasp on the IGB, slowly extract the IGB up the esophagus.
15. When the IGB reaches the upper esophageal sphincter, hyperextend the head to straighten the passage out of the esophagus and throat, allowing for an easier extraction.
16. Remove the IGB from the mouth.

14.6 IGB Replacement

If an IGB needs to be replaced, then follow the instructions for IGB Removal and IGB Placement and Filling. Additionally, it is recommended that the same volume of sterile saline that was used during the placement of the previous IGB (i.e. initial fill volume) be used when filling the replacement IGB.

CAUTION: A larger initial fill volume in the replacement IGB may result in severe nausea, vomiting or ulcer formation.

15 MEDICAL IMAGING

The saline filled IGB is considered to be MR Safe.

16 RETURNED GOODS POLICY

Authorization must be received from customer service at Apollo Endosurgery prior to return of the merchandise. Merchandise returned must have all the manufacturer's seals intact to be eligible for credit or replacement. Products returned may be subject to restocking charges.

17 DISCLAIMER OF WARRANTY AND LIMITATION OF REMEDY

There is no express or implied warranty, including without limitation any implied warranty of merchantability or fitness for a particular purpose, on the Apollo Endosurgery, Inc. product(s) described in this publication. To the fullest extent permitted by applicable law, Apollo Endosurgery, Inc. disclaims all liability for any indirect, special, incidental, or consequential damages, regardless of whether such liability is based on contract, tort, negligence, strict liability, products liability or otherwise. The sole and entire maximum liability of Apollo Endosurgery, Inc., for any reason, and buyer's sole and exclusive remedy for any cause whatsoever, shall be limited to the amount paid by the customer for the particular items purchased. No person has the authority to bind Apollo Endosurgery, Inc. to any representation or warranty except as specifically set forth herein. Descriptions or specifications in Apollo Endosurgery, Inc. printed matter, including this publication, are meant solely to generally describe the product at the time of manufacture and do not constitute any express warranties or recommendations for use of the product in specific circumstances. Apollo Endosurgery, Inc. expressly disclaims any and all liability, including all liability for any direct, indirect, special, incidental, or consequential damages, resulting from reuse of the product.

18 PRODUCT ORDERING INFORMATION

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http://apolloendo.com/

U.S. Patent: 4,930,535; 5,084,061

GRF-00346-00R09 December 2020

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19 SYMBOLS

Table 22: Symbols Used on Product Packaging

Symbol	Description
	Caution. See Instructions for Use
	Consult Instructions for Use.
	Manufacturer
	Reference Number
	Serial Number
	Non-Sterile
	MR Safe
	Use By Year, Month, & Day
	Single Use Only. Do Not Re-use.
	Authorized Representative in the European Community
	Lot Number
	Do not use if package is damaged
Rx Only	Caution: Federal law (USA) restricts this device to sale by or on the order of a physician.