ORBERA™ Intragastric Balloon System (ORBERA™)

Directions for Use (DFU)

Rx Only

Apollo Endosurgery, Inc.

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY

CONTENTS

1. INTRODUCTION

The information below is generalized. Each patient must be individually evaluated for ORBERA™ Intragastric Balloon (ORBERA™) 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 balloons and the possible benefits of a temporary treatment for weight loss prior to use of ORBERA™.

Physicians placing ORBERA™ 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 ORBERA™ training program.
- Clinical use of ORBERA™ to make ORBERA™ as 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

ORBERA™ 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 package insert. 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 balloon may be required if serious adverse reactions occur.

3. DEVICE DESCRIPTION

ORBERA™ (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

ORBERA™ is placed in the stomach and filled with saline, causing it to expand into a spherical shape (Figure 2). The filled balloon is designed to occupy space and move freely within the stomach. The expandable design of ORBERA™ permits a fill volume range of 400cc (minimum) to a maximum of 700cc (refer to section 11.2 for filling guidelines). Once filled, the ORBERA™ volume is not adjustable. A self-sealing valve permits detachment from external catheters (see Section 10 Instructions for Use).

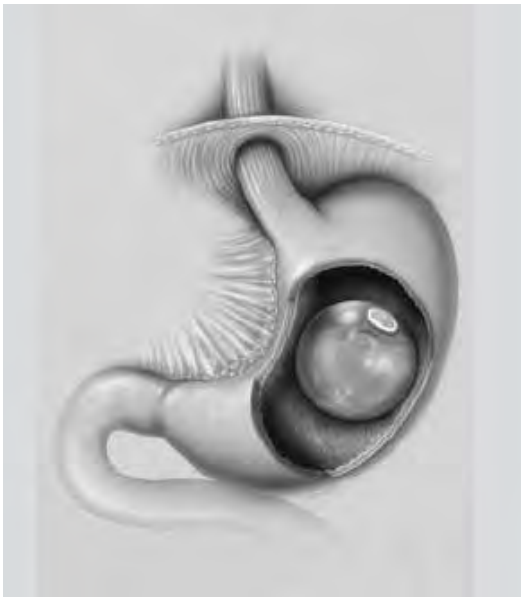


Figure 2. Saline-filled ORBERA™ in the stomach

The ORBERA™ balloon is positioned within the Placement Catheter Assembly. The Placement Catheter Assembly (Figure 3) consists of a 6.5mm external-diameter silicone catheter, one end of which is connected to a sheath in which the collapsed balloon resides. The opposite end is connected to a Luer lock connector for attachment to a filling system. Length markers are provided as a reference on the fill tube.

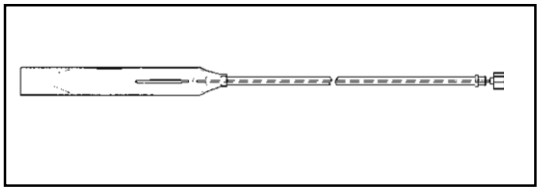


Figure 3. Placement Catheter Assembly

A guidewire has been inserted into the silicone placement catheter for increased rigidity during placement. A filling system consisting of an IV spike, fill tube and filling valve is provided to assist in the balloon deployment.

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. CONTRAINDICATIONS

- The presence of more than one intragastric balloon 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 hernia or ≤ 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 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 ORBERA™.
- 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.

6. WARNINGS

- Patients must be advised that ORBERA™ is intended to be placed for 6 months maximally, at which point removal is required. Longer periods of balloon placement increase the risk of balloon 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 balloons are filled to a larger volume than indicated (greater than 700cc).
- Patients reporting loss of satiety, increased hunger and/or weight gain should be examined endoscopically as this may be indicative of a balloon deflation.
- Deflated devices should be removed promptly. Patients should be advised that balloon 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 balloon.

- When filling the balloon during the placement procedure, avoid rapid fill rates as these will generate high pressure which can damage the ORBERA™ valve or cause premature detachment of the balloon from the placement catheter.

- Bowel obstructions have been reported due to deflated (i.e. collapsed) balloons passing into the intestines and have required surgical removal. The risk of obstructions in the small intestine 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 obstruction can result in death.

- Endoscopic removal of ORBERA™ **must** be completed in the presence of an empty stomach. Patients should be on a liquid diet for 48 hours and NPO 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.

- Proper positioning of the Placement Catheter Assembly and the ORBERA™ balloon within the stomach (using measured distance from the incisors via the insertion tube markings) is necessary to allow proper filling. Lodging of the balloon in the esophageal opening during filling may cause serious injury. Failure to confirm proper positioning may cause injury to the esophagus, duodenum, or pylorus.

- If it is necessary to replace a balloon which has spontaneously deflated (i.e. collapsed), the recommended initial fill volume of the replacement balloon is the same as for the removed balloon. A greater initial fill volume in the replacement balloon may result in severe nausea, vomiting or ulcer formation.

- ORBERA™ is composed of a soft silicone elastomer and is easily damaged by instruments or sharp objects. The balloon must be handled only with gloved hands and with the instruments recommended in Section 10.4 ORBERA™ Removal.

- 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.

- Acute pancreatitis has been reported as a result of injury to the pancreas by the balloon. Patients experiencing any symptoms of acute pancreatitis (i.e. acute abdominal pain, nausea or vomiting) should be counseled to seek immediate care.

- Spontaneous hyperinflation of an indwelling balloon with gas has been reported in patients with ORBERA indwelling balloons. Symptoms of significant balloon over-inflation include intense abdominal pain, swelling of the upper abdomen (abdominal distension) with or without discomfort, difficulty breathing, and/or vomiting. Patients experiencing any of these symptoms should be counseled to seek immediate care.

- 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 and other complications 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.

7. PRECAUTIONS

- Placement of the balloon within the stomach produces 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 balloon, 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.

- 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 ORBERA™ 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 ORBERA™ 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 ORBERA™ is in place. Other medications that are started prophylactically should be continued after ORBERA™ placement until they are no longer needed. Furthermore, subjects will be directed to avoid medications known to cause or exacerbate gastroduodenal mucosal damage.

- ORBERA™ is a silicone elastomer balloon 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 potentially prolong the integrity of the ORBERA™ balloon.

- If difficulty with the ORBERA™ fill tube is noted during placement (e.g., resistance to balloon filling), then the device should be removed and replaced with a new balloon. To lessen, or prevent fill tube defects, during the filling process the fill tube must remain slack. If the fill tube is under tension during this process, the fill tube may dislodge from the balloon, preventing further balloon deployment.

- The physiological response of the patient to the presence of ORBERA™ 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.

- A patient whose deflated (i.e. collapsed) balloon has moved into their intestines must be monitored closely for an appropriate period of time (at least 2 weeks) to confirm its uneventful passage through the intestine.

- The ORBERA™ Intragastric Balloon has not been studied on individuals who have a patulous pylorus, active *H. pylori* infection, and subjects with either symptoms or a diagnosis of delayed gastric emptying.

- 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 balloon, 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.

- Patients taking anti-cholinergic medications or psychotropic medications know to delay gastric emptying.

8. 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 Orbera Intragastric Balloon specifically, and the risks associated with the patient's degree of intolerance to a foreign object placed in the stomach.

8.1 Possible Adverse Events

Possible adverse events of the use of ORBERA™ include:

- Intestinal obstruction by the balloon. An insufficiently filled balloon or a leaking balloon 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, as may occur after prior surgery on the bowel or adhesion formation, the balloon may not pass and then may cause a bowel obstruction. If this occurs, surgery or endoscopic removal could be required.

- Death due to adverse events related to intestinal obstruction is possible.

- Esophageal obstruction. Once the balloon is being filled in the stomach, the balloon could be inadvertently pulled back into the esophagus. If this occurs, surgery or endoscopic removal could be required.

- Gastric outlet obstruction. A partially-filled balloon (i.e., <400 cc), or a leaking balloon could lead to gastric outlet obstruction, requiring balloon removal. It is also possible for a fully filled

(400-700 cc) balloon 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 balloon into the antrum.
- Injury to the digestive tract during placement of the balloon 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 balloon placement as the digestive system adjusts to the presence of the balloon.
- Continuing nausea and vomiting. This could result from direct irritation of the lining of the stomach, delayed gastric emptying and/or the balloon blocking the outlet of the stomach. It is even theoretically possible that the balloon 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 balloon. 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 balloon, 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.
- Balloon deflation (i.e. collapse) and subsequent replacement.
- Acute pancreatitis.
- Spontaneous hyperinflation due to gas production within the balloon.

8.2 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.

8.3 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 a balloon placed, removed, and another balloon placed. In all subjects the balloon 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 9.0 (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 balloon 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 2. All 3 procedure-related SAEs that occurred in the U.S. pivotal study are included in Table 3. 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, balloon 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 1 below.

Table 1. Reported Occurrence Rates in the U.S. for Selected Adverse Events

Adverse Events	Count	Rate
Spontaneous Hyperinflation	52	0.320%
Acute Pancreatitis	10	0.061%
Esophageal Perforation	4	0.025%
Gastric Perforation (Stomach Perforation)	12	0.074%
Aspiration	12	0.074%
Death	4	0.025%
Total	**95**	**0.584%**
ORBERA™ (B-4800) and BIB Accessories Unit Sold in United States from August 05, 2015 (PMA) through January 31, 2019	**16,265**	

† Some complaints were counted more than once within a category due to multiple events reported. 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 2. 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 balloon 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:
     a. Resulted in a life-threatening illness or injury,
     b. Resulted in a permanent impairment of a body function or body structure,
     c. Required in-patient hospitalization or prolonged hospitalization,
     d. Resulted in medical or surgical intervention to prevent permanent impairment to a body function or body structure,
     e. 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 3. 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 balloon removal Dissection: During balloon placement	Tear and dissection: Hospitalization - injury resolved	0
Laryngospasm	1 out of 160 (.63%)	1	During balloon placement	Intubation	0

1. A serious adverse event is one that:
   - Led to death,
   - Led to a serious deterioration in the health of a patient that:
     f. Resulted in a life-threatening illness or injury,
     g. Resulted in a permanent impairment of a body function or body structure,
     h. Required in-patient hospitalization or prolonged hospitalization,
     i. Resulted in medical or surgical intervention to prevent permanent impairment to a body function or body structure,
     j. 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 4.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 4. 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 5, 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 5. 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 (.37%)	0 (0%)
Alopecia	2 (1.3%)	2 (.37%)	0 (0%)
Anemia	2 (1.3%)	2 (0.25%)	0 (0%)
Anxiety	2 (1.3%)	2 (0.25%)	0 (0%)
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%)
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

9. CLINICAL STUDIES

9.1 ORBERA™ U.S. Pivotal Study

9.1.1 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.

9.1.2 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.

9.1.3 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 6.

Table 6. Subject Demographics and Baseline Characteristics (N = 255 Subjects)

Demographics[1]	Category	ORBERA™ (n = 125) n	(%)	Control (n = 130) n	(%)
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)	

Demographics[1]	Category	ORBERA™ (n = 125) n	(%)	Control (n = 130) n	(%)
	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/m²)[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

9.1.4 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 7 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 8 shows

responder rates at these same timepoints with responders defined as achieving at least 5%, 7%, and 10% TBWL (mITT with LOCF).

Table 7. 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 8. 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 9.

Table 9. 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 10.

Table 10. 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 Tables 11.

Table 11. 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 12. 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 12. 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.

9.2 Global Product Experience and Clinical Studies

ORBERA™ has been approved in many countries since the 1990's. As of January 31, 2019 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 8,036 complaints spanning a period from January 1, 2008 to January 31, 2019 are presented in Table 13; 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 13. ORBERA™ device- and procedure- related adverse events and complaints reported through clinical product surveillance[1] between January 1, 2008 and January 31, 2019

Events	†Count	††Rate
Difficulty with fill tube or difficulty adding/removing saline	1,311	0.42%
Broken device	1,247	0.40%
Vomiting	939	0.30%
Pain	821	0.27%
Device deflation	779	0.25%
Nausea	594	0.19%
*Other	437	0.14%
Spontaneous hyperinflation	287	0.09%
Reflux	251	0.08%
Intolerance	197	0.06%
Obstruction or bowel complications	188	0.06%
Irritation/inflammation	162	0.05%
Unsatisfactory weight loss	138	0.04%
Dehydration	113	0.04%
Leak(s)	95	0.03%
Surgery related observation or complication	68	0.02%
Infection	61	0.02%
Ulcer or gastric erosion	52	0.02%
Stomach perforation	49	0.02%
Unsuccessful placement	30	0.01%
Death	29	0.01%
Cardiopulmonary complication and dyspnea	24	0.01%
Pancreatitis	22	0.01%
Dysphagia	21	0.01%
Vessel damage/bleeding or hemorrhage	20	0.01%
Delayed Gastric Emptying	19	0.01%
Aspiration	18	0.01%
Erosion	13	0.00%
Necrosis	13	0.00%
Esophageal perforation	11	0.00%
Device visibility or palpability	12	0.00%
Varied injuries	12	0.00%
Device displacement or migration	10	0.00%
Hernia	4	0.00%
Respiratory Disorder	4	0.00%
Ischemia	4	0.00%
Pulmonary Embolism	4	0.00%

Events	†Count	††Rate
Allergic reaction	1	0.00%
Myocardial infarction	1	0.00%
Total	**8,062**	**2.61%**

† Some complaints were counted more than once within a category due to multiple events reported. 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.

†† The event rate represents the counts of an event divided by the number of devices distributed as of the reporting cut-off on January 31, 2018. Note that the number of devices distributed may be greater than the number of devices placed.

*Includes Abdominal Distension, Belching, Bloating, Burping, Constipation, Cramping, Dehydration, Delayed Gastric Emptying, Diarrhea, Gas, Gastroparesis, Gastritis, Hiccups, Loss of appetite/ Not feeling full, Low/High Lipase (or) Potassium level, and Sore Throat.

Two sponsor-initiated clinical trials were conducted outside of the U.S., one in France (n=36 treatment subjects), described in section 9.2.1, and one in Australia (n=74, 37 treatment and 37 control subjects), described in section 9.2.2. The adverse event profile for these two studies was 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.

9.2.1 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.

9.2.2 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 on 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%). The majority of 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.

10. INSTRUCTIONS FOR USE

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

DO NOT REMOVE THE BALLOON FROM THE PLACEMENT CATHETER ASSEMBLY.

A filling system is provided to assist in the balloon deployment.

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

10.1 Balloon 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 balloon gently down the esophagus and into the stomach. The small size of the Placement Catheter Assembly allows ample space for the endoscope to be reinserted for observing the balloon filling steps.

When it has been confirmed that the balloon is below the lower esophageal sphincter and well within the stomach cavity, remove the guidewire.

Fill the balloon with sterile saline. An aseptic technique, similar to changing IV fluids, is recommended in order to avoid contaminating the saline within the balloon with micro-organisms that may lead to eventual gaseous enlargement of the balloon. Place the filling system spike into the sterile saline bag. Attach a syringe to the filling system valve and prime the filling system. Connect the Luer-Lock connector on the fill tube to the filling system valve. Proceed to deploy the balloon, verifying with the endoscope that the balloon is within the stomach.

CAUTION: During the filling process the fill tube must remain slack. If the fill tube is under tension during this process the fill tube may dislodge from the balloon preventing further balloon deployment.

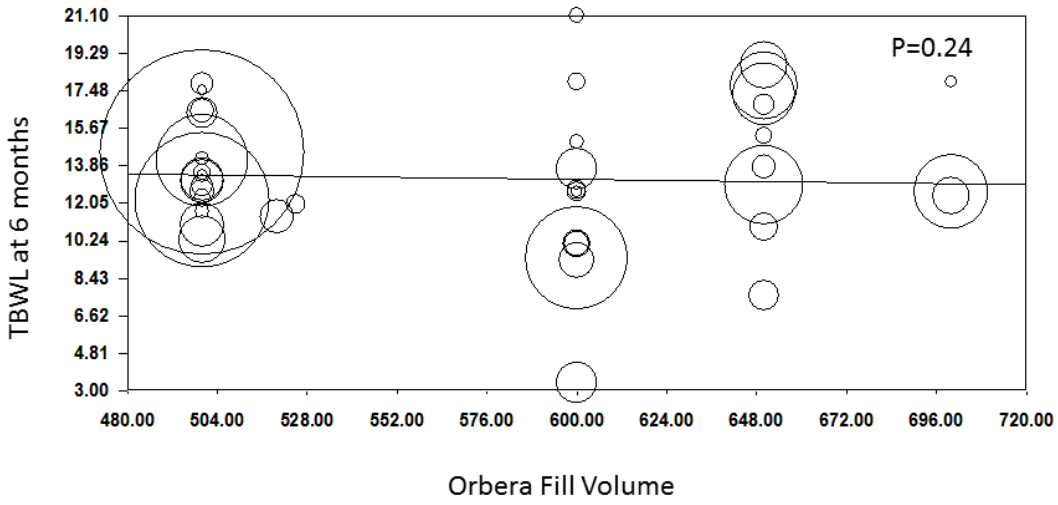
WARNING: Rapid fill rates will generate high pressure which can damage the ORBERA™ valve or cause premature detachment.

10.1.1 Filling Recommendations

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

To determine ideal balloon 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.1 Figure 4, meta-regression analysis of balloon 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).2 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 ± 50 cc.

Figure 4. Meta-regression analysis of balloon fill volume correlation with total body weight loss (TBWL). [2]



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 valve damage or premature detachment:

- Always use the ORBERA™ fill kit provided.
- Always use a 50 cc syringe to fill the ORBERA™. Use of smaller syringes can result in very high pressures of 30, 40, and even 50 psi, which can damage the valve.

- With a 50 cc syringe, each filling stroke should be done slowly (minimum of 10 seconds) and steadily. Slow, steady filling will avoid the generation of high pressure in the valve.
    - **WARNING:** Rapid fill rates will generate high pressure which can damage the ORBERA™ valve or cause premature detachment.
    - Filling should always be completed under direct visualization (gastroscopy). Integrity of the valve should be confirmed by observing the valve lumen as the balloon fill tube is removed from the valve. A balloon with a leaking valve must be removed immediately. A partially filled balloon can result in a bowel obstruction, which can result in death. Bowel obstructions have occurred as a result of unrecognized or untreated balloon deflation (i.e. collapse).

NOTE: Any balloons which 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 400 mL is required for the balloon to deploy completely from the placement assembly. After filling the balloon, remove the fill kit from the fill tube. To seal the balloon valve, connect a syringe directly to the fill tube Luer-Lock and produce a gentle suction on the placement catheter by withdrawing the plunger of the syringe. You will not withdraw fluid as the valve will seal with the vacuum created.

CAUTION: If more than 5 cc of fluid can be removed from the balloon, replace the balloon. Fluid cannot be removed from the balloon using the fill tube because the tip of the fill tube does not extend to the end of the valve.

When filled, the balloon is released by pulling the fill tube gently while the balloon is against the tip of the endoscope or the lower esophageal sphincter.

Continue to pull the fill tube until it is out of the self-sealing valve. After release, the balloon should be visually inspected.

10.1 ORBERA™ Placement and Filling (Step-by-Step)

1. Prepare the patient according to hospital protocol for sedation and endoscopy.
2. Perform endoscopic inspection of esophagus and stomach.
3. Remove endoscope.
4. Where there are no contraindications:
    a. Lubricate the ORBERA™ placement sheath with surgical lube-gel.
    b. Move the ORBERA™ gently into the esophagus and into the stomach.
5. Reinsert the endoscope while the balloon is in situ to observe filling steps. The balloon must be below the lower esophageal sphincter and well within the stomach cavity.
6. Remove the guidewire from the fill tube.

7. Attach the 3-way stopcock and 50 cc syringe to the Luer-Lock. Insert filling kit spike into a bag of sterile normal saline solution for injection (.9 NS).
8. Slowly fill the balloon with sterile saline, 50 cc at a time. Repeat up to 700 cc (14 strokes). Recommended maximum volume is up to 700 cc; minimum fill volume is 400 cc.
9. After the last stroke pull back on plunger to create a vacuum in the valve to ensure closure.
10. Gently pull the tubing out and check valve for leakage.

10.2 ORBERA™ Removal (Step-by-Step)

1. Ensure that the patient has been on a liquid diet for 72 hours and NPO for a minimum of 12 hours prior to attempted 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 succession splash should be performed, followed by radiographic evaluation if succession splash is absent and epigastrium full or tender. If radiographic evaluation is positive for distended stomach with or without an antral balloon, 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.
3. Insert the endoscope into the patient's stomach.
4. Assess for 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 balloon through the endoscope.
6. Insert a sheathed needle catheter down the working channel of the endoscope.
7. Use the advanced exposed needle to puncture the balloon.
8. Push the needle catheter through the balloon shell well into the balloon.
9. Remove the needle from the catheter.
10. Apply suction to the deeply inserted catheter until all fluid is evacuated from the balloon.
11. Remove the catheter from the balloon 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 balloon with the grasper (ideally at the opposite end of valve if possible).
14. Consider administering a smooth muscle relaxant such as intravenous glucagon to relax the lower esophageal sphincter.
15. With a firm grasp on the balloon, slowly extract the balloon up the esophagus.
16. When the balloon reaches the upper esophageal sphincter, hyperextend the head to straighten the passage out of the esophagus and throat, allowing for an easier extraction.

17. Remove the balloon from the mouth.

10.3 Balloon Replacement

If a balloon needs to be replaced, the instructions for ORBERA™ Removal and ORBERA™ Placement and Filling are followed. The recommended initial fill volume of the replacement balloon is the same as the initial fill volume of the removed balloon.

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

11 HOW SUPPLIED

Each ORBERA™ contains a balloon positioned in a Placement Catheter Assembly. All are supplied NON-STERILE and FOR SINGLE USE ONLY. All components should be handled carefully.

11.1 Cleaning Instructions

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

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 tissue reaction.

12 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.

13 DISCLAIMER OF WARRANTY AND LIMITATION OF REMEDY

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14 PRODUCT ORDERING INFORMATION

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http://apolloendo.com/

The ORBERA™ Intragastric Balloon contains no latex or natural rubber materials

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

GRF-00346-00R07 June 2019

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