SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Intragastric Balloon

Device Trade Name: ORBERA™ Intragastric Balloon System

Device Procode: LTI

Applicant's Name and Address: Apollo Endosurgery, Inc.
1120 S Capital of Texas Hwy
Building 1, Suite 300
Austin, TX 78746

Dates of Panel Recommendations: None

Premarket Approval Application (PMA) Number: P140008

Date of FDA Notice of Approval: August 5, 2015

II. 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.

III. CONTRAINDICATIONS

ORBERA™ is contraindicated for the following:

- The presence of more than one Intragastric Balloon at the same time.
- Prior gastrointestinal 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 or a hernia > 5cm 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 or any other severe motility disorder that that may pose a safety risk during removal of the device.

- Severe coagulopathy

- Hepatic insufficiency

- Gastric mass.

- Severe coagulopathy

- Hepatic insufficiency or cirrhosis

- Patients who are known to have or suspected to have an allergic reaction to materials contained in the ORBERA™ system.

- Any other medical condition which 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ORBERA™ Intragastric Balloon System device labeling.

V. DEVICE DESCRIPTION

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

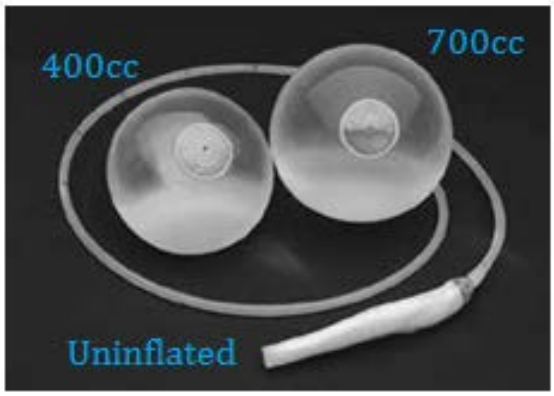

Figure 1: ORBERA™ filled to 400cc, 700cc, and the unfilled system in the foreground

ORBERA™ is a non-pharmaceutical, non-surgical aid designed to assist weight loss by partially filling the stomach. ORBERA™ consists of a soft, smooth silicone elastomer balloon that is placed in the stomach endoscopically and filled with saline, causing it to expand into a spherical shape. The filled balloon is designed to occupy space and move freely within the stomach (Figure 2). The expandable design of ORBERA™ permits an initial fill volume range of 400cc (minimum) to a maximum of 700cc. Once filled, the ORBERA™ volume is not adjustable. A self-sealing valve permits detachment of the balloon from external catheters used during the ORBERA™ placement procedure.

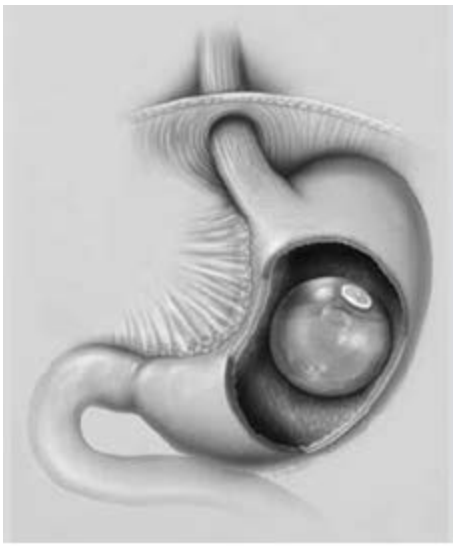

Figure 2: Saline-filled ORBERA™ in the stomach

In the ORBERA™ System, the intragastric 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 for reference on the fill tube.

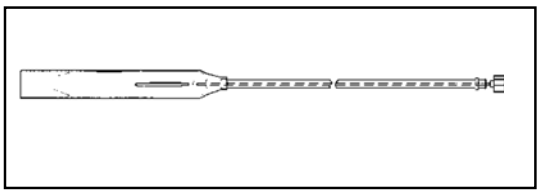

Figure 3: Placement Catheter Assembly

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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternative for the treatment of obesity (BMI of >30 kg/m^2), which can be divided in to the following: non-surgical treatments, medical devices (gastric bands and vagal blockers), and surgery. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

a. Non-Surgical Treatments (Medical Therapy):

- Diet, exercise, and behavior modification programs
- Prescription weight loss medications

- Other procedures and practices, such as jaw-wiring, hypnosis, counseling, psychotherapy, nutritional supplements, etc.

Several reports have suggested a rather high incidence of failure for obese patients to sustain long-term weight loss with any form of non-surgical treatment.

a. Obesity Surgery

Bariatric surgery is generally reserved for patients with BMI > 35 kg/m² with one or more obesity-related comorbid decisions.

Bariatric surgery includes techniques include roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy, and the biliopancreatic diversion with duodenal switch. RYGB reduces your stomach to the size of a small pouch by stapling off a section of it. An outlet is then created which attaches the proximal gastric pouch to the small intestine, bypassing most of the stomach and the upper part of the small intestine. This procedure has a malabsorptive component.

Vertical sleeve gastrectomy recues the size of your stomach by surgically removing a large portion of it. Unlike RYGB, the stomach is not bypassed and there is no malabsorption component.

The biliopancreatic diversion with duodenal switch is a procedure in which stomach removal is restricted to the outer margin, leaving a stomach sleeve with the pylorus intact. The small intestine is divided with one end attached to the stomach pouch. The majority of the small intestine is bypassed causing nearly complete malabsorption.

b. Medical Devices

Medical devices used in the treatment of obesity include gastric bands and vagal blockers. Gastric bands are indicated for patients with a BMI of at least 40 kg/m2, or a BMI of at least 30 kg/m^2 with one or more obesity-related comorbid conditions, who have failed more conservative weight reduction alternatives. Laparoscopic vagal blocking therapy is indicated for use in weight reduction in patients aged 18 years through adulthood who have a BMI of 40 to 45 kg/m2, or a BMI of 35 to 39.9 kg/m^2 with one or more obesity related co-morbid conditions, and have failed at least one supervised weight management program within the past five (5) years.

VII. MARKETING HISTORY

ORBERA™ received CE-mark in Europe in 1997 under the name BioEnterics® Intragastric Balloon (BIB®). As of August 31, 2014 over 220,000 ORBERA™ devices have been distributed to over 80 countries with ORBERA™ approval. These include countries from Europe, Africa, Middle East, Latin America, Asia Pacific, and Canada. The ORBERA™ has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Complications that may result from the use of ORBERA™ include the risks associated with the medications and methods utilized in the endoscopic procedure, the risks associated with any endoscopic procedure, and the patient's degree of intolerance to a foreign object placed in the stomach.

Potential risks associated with upper endoscopic procedures include, but are not limited to: abdominal cramping and discomfort from the air used to distend the stomach, sore or irritated throat, bleeding, infection, tearing of the esophagus or stomach, and aspiration pneumonia. The most common complications involve with sedation include 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.

Potential risks associated with the device include ulcerations/erosions, balloon deflation/migration gastric outlet or intestinal obstruction esophageal perforation, abdominal pain, nausea, vomiting, gastroesophageal reflux, bloating, belching, dysphagia, and dehydration.

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Physical Characterization

The physical properties of ORBERA™ have been tested and characterized. Testing performed on the components of the device, summarized in Table 1.

Table 1: Physical Testing Conducted on ORBERA™ System

Test	Purpose	Acceptance Criteria	Result
Deployment Testing/Fill Testing at 30 psi	To test the ability of the assembly to deploy at the minimum inflation volume and not burst at the maximum inflation volume at the specified low inflation pressure.	Assemblies deploy at volumes less than 400cc. Assemblies do not burst at volumes less than 700cc. Valves allow for continuous flow at low pressure (30 psi).	PASS
Deployment Testing/Fill	To test the ability of the assembly to deploy at the	Assemblies deploy at volumes less than 400cc. Assemblies do not burst at volumes less than	PASS

Test	Purpose	Acceptance Criteria	Result
Testing at 40 psi	minimum inflation volume and not burst at the maximum inflation volume at the specified high inflation pressure. To test the ability of the fill tube to remain engaged in the valve at high inflation pressure.	700cc. Fill tubes do not dislodge from valves at high pressure (40psi).	
Fill Tip Removal Force Testing	To test the force of the fill tip to dislodge from the assembly and show it is less than the anticipated force to damage the GE junction during fill tube removal from the patient.	Peak force must be no greater than 4 lbf so that damage to the GE junction does not occur.	PASS
Leak Testing	To test the ability of the valve to close and hold fluid after fill tube removal. To test the ability of the balloon to maintain volume over time.	No valves seeping water after 5 minutes. No balloons lose more than 5% of their initial weight after one week.	PASS
Valve to Shell Bond Testing	To test the integrity of the valve/shell bond per ASTM F703 and ASTM F1441.	Samples withstand the 200% elongation for 10 seconds without delamination or tearing.	PASS
Radio-Opacity Evaluation	To show the ability of the balloon valve to be located via X-ray.	Expert surgeons had to agree that the radio-opacity of the valve was acceptable based on current radiological techniques.	PASS

Test	Purpose	Acceptance Criteria	Result
Bond Strength Between Fill Tube and Sheath	To test the integrity of the bond between the fill tube and sheath.	The pull strength for the bond between the fill tube and the sheath must be 3.5 lbf or greater.	PASS
Static Shell Tensile Testing	To test the tensile force of the shell per ASTM F703 and F1441.	Per ASTM F703 and F1441, tensile strength of the shell is be at 2.5 lbf or greater.	PASS
Balloon Deflation Puncture Test	To test the ability of the balloon shell to be punctured for deflation.	The puncture force is less than or equal to that of the shells made of methyl silicone (measured at .375 lbf), the material previously used for the commercialization balloon.	PASS
Valve Patch to Valve Stem Testing	To test the bond strength of the valve patch to stem.	The bond strength of the valve patch to the valve stem must be 5 lbf.	PASS
Elongation and Tensile Strength of Fill Tube	To test the fill tube elongation.	The fill tube elongation should be 30% or less when the tubing is pulled to 4 lbf. to minimize tubing backlash.	PASS
Fill Tube Break Force	To show the fill tube break force is greater than the force to remove the fill tube from the balloon.	The fill tube break force should be greater than 12 lbf, minimum.	PASS
Bond Strength of Luer Connector to Fill Tube Bond	To test the luer/fill tube bond to a 1.5x factor of safety compare to the fill tube removal force (4 lbf).	The force required to pull the luer connector from the fill tube is 6 lbf or greater.	PASS

Test	Purpose	Acceptance Criteria	Result
Tensile Force to Remove the Fill Tube Tip from Tube	To test the fill tip removal force from the fill tube and show it is greater than the force to remove the fill tip from the balloon.	The pull force required to pull the fill tube tip from the fill tube is 6 lbf or greater.	PASS
Bond Strength of Guidewire to Luer	To show the bond strength of the guidewire to luer is higher than the force to remove the guidewire from the fill tube.	The force required to pull the guidewire from the luer connector is 0.75 lbf or greater.	PASS
Packaging, Storage, and Shelf Life Testing	To test the ability of the device to deploy at the minimum fill volume when subjected to 2 years of accelerated aging and typical shipping conditions.	Test consisted of shipping ORBERA Systems from California to a vendor in the Netherlands and then assessing that the balloons would deploy from the sheath when filled with 400mL of saline. Shelf life testing includes evaluation of finished devices subjected to two (2) year accelerated aging.	PASS

B. Biocompatibility Testing

The biocompatibility and toxicity testing were selected according to ISO 10993-1, "Biological Evaluation of Medical Devices Part 1: Guidance on Selection of Tests." The testing reported herein was conducted according to ISO 10993, as described below, and in compliance with 21 CFR Part 58 Good Laboratory Practices Regulations.

ORBERA™ is placed in the stomach for a period up to six (6) months and is categorized as a mucosal contacting, surface device with permanent exposure (30 days). However, for purposes of planning the ISO 10993 testing, the system was considered a permanent implant (> 30 days) with surface mucosal membrane contact. Table 2 summarizes the tests performed to comply with the ISO 10993 Biocompatibility test requirements.

Table 2: Summary of Biocompatibility Testing on the ORBERA™ System

ISO 10993 Series	Compliance with ISO 10993-1:2009/AC: 2010	
	Balloon Assembly	**Fill Tube Assembly**
ISO 10993-1:2009/AC: 2010 Evaluation and testing within a risk management process	Current assessment complies with ISO 10993-1:2009/AC: 2010.	Current assessment complies with ISO 10993-1:2009/AC: 2010.
ISO 10993-3:2014 Tests for genotoxicity, carcinogenicity and reproductive toxicity	The requirements and intent of the standard were met.	NA
ISO 10993-5:2009 Tests for *in vitro* cytotoxicity	Testing meets current standard.	Testing meets current standard.
ISO 10993-6:2007 Tests for local effects after implantation	Testing meets current standard.	NA
ISO 10993-10:2010 Tests for irritation and delayed-type hypersensitivity	Testing meets current standard.	Testing meets current standard.
ISO 10993-11:2006 Tests for systemic toxicity	NA	NA
ISO 10993-12:2012 Sample preparation and reference materials	Testing meets current standard.	Testing meets current standard.
ISO 10993-13:2010 Identification and quantification of degradation products from polymeric medical devices	Testing meets current standard.	Testing meets current standard.
ISO 10993-17:2002 Establishment of allowable limits for leachable substances	Testing meets current standard.	Testing meets current standard.
ISO 10993-18:2005 Chemical characterization of materials	Testing meets current standard.	Testing meets current standards.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the ORBERA™ Intragastric Balloon System for Body Mass Index (BMI) ≥ 30 and ≤ 40 kg/m when used in conjunction with a long-term supervised diet and behavior modification program designed to increase the possibility of long-term weight loss maintenance in the US under IDE # G040001. Data from this clinical study were the basis for the PMA approval decision. Global data, presented in section XI, was also reviewed to determine the safety of the device. A summary of the clinical study is presented below.

A. Study Design

The pivotal study of ORBERA™, known as IB-005, was a multicenter, prospective, randomized, non-blinded comparative study. Subjects from 15 U.S. investigational sites were enrolled between June 20, 2008 and October 10, 2010. The database for this PMA reflected data collected through October 28, 2011 and included 448 subjects.

Subjects with obesity (BMI $\geq$ 30 and $\leq$ 40 kg/m^2) who met all the inclusion criteria and no exclusion criteria were randomized to the ORBERA™ treatment group or control group in a 1:1 ratio. Subjects randomized to the treatment group participated in a 12-month behavioral modification program, the first 6 months with ORBERA™ in place plus the 6 months following ORBERA™ removal. Subjects randomized to the control group participated in the 12-month behavioral modification program alone.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the IB-005 study was limited to patients who met the following inclusion criteria:

- Had a BMI $\geq$ 30 kg/m^2 and $\leq$ 40 kg/m^2
- Male or female, between 18 and 65 years of age, inclusive
- Had a history of obesity (BMI $\geq$ 30 kg/m^2) for at least 2 years and had failed more conservative weight-reduction alternatives, such as supervised diet, exercise, and behavioral modification programs
- Were willing to commit to a long-term low calorie (1000-1500 calories/day) supervised diet
- Had reasonable weight loss expectations (accepted a goal of losing up to 15% of body weight after 26 weeks)
- Were able to follow requirements outlined in the protocol, including complying with the visit schedule and behavioral modification program, and was willing to undergo protocol-specific procedures (e.g., endoscopy, local sedation, general anesthesia, upper gastrointestinal radiography (UGI), electrocardiography (EKG), GE study, and/or clinical laboratory testing)
- Were willing to take prescribed proton pump inhibitors (PPIs) and other medications as prescribed by the investigator
- Were able to provide written informed consent
- Were able to provide written Authorization for Use and Release of Health and Research Study Information
- Had successful completion of the pre-placement screening, educational programs and psychological assessment supporting that the subject was an appropriate study candidate
- Were willing to use contraception (e.g., birth control pills, condoms, abstinence) and avoid pregnancy during the study if female of childbearing potential

Patients were not permitted to enroll in the IB-005 study if they met any of the following exclusion criteria:

- Any surgery of the foregut excluding uncomplicated cholecystectomy
- History of gastrointestinal (GI) surgery (excluding uncomplicated appendectomy), GI obstruction, adhesive peritonitis, and/or hiatal hernia (≥ 2 cm)
- A patulous pyloric channel
- History or symptoms of esophageal or GI motility disorders as these patients are particularly susceptible to the development of esophagitis
- History or previous symptoms of delayed GE and/or delayed GE having been documented on a previously performed gastric scintigraphy study or another previously performed diagnostic study such as an UGI x-ray series
- Current symptoms of delayed GE
- A history of myocardial infarction in the previous 6 months: New York Heart Associate (NYHA) Class III or IV (heart failure) or cardiac arrhythmia (e.g., atrial fibrillation)
- Anemia: defined as a hemoglobin value for females of <11.3 g/dL; for males <13.0 g/dL
- History or symptoms of varices, bowel obstruction, congenital or acquired GI anomalies (e.g., atresias, stenosis, stricture, and/or diverticula), severe renal, hepatic, and/or pulmonary disease
- History or symptoms of inflammatory bowel disease, such as Crohn's disease or ulcerative colitis
- History or symptoms of uncontrolled or unstable thyroid disease
- Subjects with a positive test for *Helicobacter pylori (H.p.)* at screening; subjects were able to participate in the study if, prior to randomization, they were treated with a pharmacological regimen designed to eradicate their *H.p.* and subsequently had a negative *H.p.* breath test indicating that the *H.p.* had been eradicated
- History or symptoms in the past 24 months of significant irritable bowel syndrome, peritonitis, active esophagitis, gastritis and/or duodenitis, gastric or duodenal ulceration, GI hemorrhage, or GI bleeding
- Type I diabetes
- Placement of previous intragastric balloon or similar device
- Ongoing treatment with anticoagulants, steroids, aspirin, non-steroidal anti-inflammatory drugs (NSAIDS), or other medications known to be gastroduodenal mucosal irritants or to reduce GI motility, and/or an unwillingness to discontinue the use of these concomitant medications
- Concomitant use of prescription, non-prescription, or over-the-counter weight loss medications or supplements at any time during the study
- Evidence of untreated psychiatric or eating disorders, such as major depression, schizophrenia, substance abuse, binge eating disorder, or bulimia
- Pregnancy, breastfeeding, or intention of becoming pregnant during the study (if female of childbearing potential)
- Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
- Poor general health, presence of a specific condition, or was in a situation which, in the Evaluating and/or Placing Investigator's opinion, may have put the subject at significant risk, may have confounded the study results, may have increased the

risks associated with endoscopy and/or placement of the ORBERA™, or may have interfered significantly with the subject's participation in the study (e.g., HIV, Hepatitis C, or cancer history within the last 5 years)

2. Follow-up Schedule

Follow-up office visits occurred at Days 1 (control group had a telephone visit at Day 1), 4, and 10 and Weeks 1, 2, 4, 8, 12, 16, 20, and 24. ORBERA™ was removed at Week 26, with 6 additional follow-up visits up to Week 39 and 6 more visits after Week 39 for a total of 26 visits throughout the study.

The objective parameters measured during the study included weight, BMI, waist and hip measurements, vital signs, concomitant medications, laboratory values, quality of life (using SF-36 and IWQOL-Lite), depressive symptoms (using BDI-II), and eating behaviors (using QEWP-R).

3. Clinical Endpoints

With regards to safety, the incidence, frequency, and severity of adverse events (AEs) related to treatment were the safety measures.

With regards to effectiveness, there were two (2) co-primary effectiveness measures:

a) The mean percent excess weight loss (%EWL) of the ORBERA™ treatment group at Month 9, and

b) The percent of ORBERA™ treated subjects with significantly greater weight loss than the control group at Month 9 (where significantly greater weight loss was defined as ≥ 15% EWL over the mean %EWL of the control group).

The study was successful if, at Month 9, the ORBERA™ group achieved at least 25% EWL and 30% of ORBERA™ treated subjects had statistically 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:

a) The change in status of comorbid conditions of Type 2 diabetes, hypertension, and dyslipidemia at Month 9, as measured by laboratory tests and vital signs, and

b) 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 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.

4. Statistical Analysis Plan

Effectiveness: The first co-primary effectiveness endpoint was mean %EWL at 9 months post ORBERA™ placement. The expectation was that ORBERA™ treated subjects would, on average, experience at least 25% EWL. The hypothesis was evaluated using Wilcoxon signed-rank one-sample test. The second co-primary effectiveness endpoint of percentage of ORBERA™ treated subjects with statistically significantly greater weight loss than the control group at 9 months was evaluated using a two-tailed exact binomial test. All other effectiveness analyses were conducted by reporting descriptive statistics along with 95% confidence intervals.

Safety: The safety endpoints were tabulated and presented at each of the follow-up time points as well as overall. Exact 95% binomial confidence limits were provided; no statistical hypotheses were evaluated.

B. Accountability of PMA Cohort

A total of 448 subjects were enrolled in the study: 131 were screen failures primarily due to ineligibility and 273 were randomized per protocol, 18 of whom discontinued prior to treatment. There were an additional 44 run-in subjects (non-randomized, mentored cases to allow physicians to gain experience with ORBERA™ procedures), 9 of whom discontinued before treatment. Of the randomized subjects, 125 were randomized to the treatment group and 130 were randomized to the control group. At the time of database lock, 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 (Month 12) and are available for analysis.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a weight loss study performed in the US.

Subjects in the ORBERA™ treatment 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 3.

Table 3: 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
	20-29	21	16.8%	18	13.8%
	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]	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

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 125 ORBERA™ subjects and 35 run-in patients who reached the 9 month study endpoint, 3 months after device removal. The key safety outcomes and adverse effects are reported in Tables 4 to 8.

Adverse effects that occurred in the PMA clinical study:

One hundred twenty-five (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.

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 (SAEs) resulting in a SAE rate of 10% (16/160, 95% CI). Eleven (11) 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 two (2) procedure-related SAEs. All device and procedure-related SAEs in both the treatment and run-in groups resolved without sequelae.

Thirty (30) out of 160 (18.8%) ORBERA™-treated subjects had their balloon removed endoscopically prior to 6 months. Eight (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.

All device-related SAEs that occurred in the U.S. pivotal study (IB-005) are included in Table 4.

Eight (8) of the 14 device related SAEs were due to device intolerance and are broken down by subject in Table 5. All procedure-related SAEs that occurred in the U.S. pivotal study (IB-005) are included in Table 6. 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.

Table 4. 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%)

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)**
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 (0.63%)	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 5. Adverse Event(s) occurring in Subjects with Device Intolerance leading to ORBERA™ Removal Prior to 6 Months

Subject	Adverse Event(s)	Study Day at Device Removal	Study Day at Study Exit
A	Dehydration and gastroesophageal reflux	41	239
B	Gastroesophageal reflux, nausea and vomiting	79	299
C	Abdominal pain, vomiting, and ketones in the urine	8	8
D	Abdominal pain, and vomiting	11	129
E	Asthenia, dyspepsia, nausea, and vomiting	3	196
F	Nausea and vomiting	60	60
G	Abdominal pain, dehydration, nausea, and vomiting	1	1
H	Nausea and vomiting	60	60

Table 6. 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	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)	During procedure	0
Laryngospasm	1 out of 160 (0.63%)	1	During procedure	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 7. 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 7. 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%)
Gastroesophageal 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 modified Intent-to-Treat 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 an early protocol 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 8, 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 (24) events (5.6%) were severe.

Table 8. 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 (general)	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%)

Preferred Terms	**#Subjects with Events (% of Subjects)**	**#Events (Frequency %)**	**#Subjects with Event Occurrence >1 (% Occurrence)**
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%)

Preferred Terms	**#Subjects with Events (% of Subjects)**	**#Events (Frequency %)**	**#Subjects with Event Occurrence >1 (% Occurrence)**
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**	

2. Effectiveness Results

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 Ideal Body Weight

(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, which was six (6) months after removal of the device. Table 9 shows weight loss at key time points 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. Table 10 shows responder rates at these same timepoints with responders defined as achieving at least 5%, 7%, and 10% TBWL.

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

Weight Loss Measure	Group[a]	Month 6		Month 9		Month 12	
		Responder rate n (%)	P-value[b]	Responder rate n (%)	P-value[b]	Responder rate n (%)	P-value[b]
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 are comparison between treatment using a chi-square test.

Some weight regain was seen in the ORBERA™ group after device removal, as seen in Table 10 above; however, much of the initial weight loss was maintained through Month 12 (six (6) 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™ and Control groups can be seen Table 11.

Table 11: 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 12.

Table12. 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, which evaluates eight (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 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 13.

Table 13: SF-36 Health Survey Mean Scores at Baseline and Month 9 by Study Group (mITT with LOCF)

	ORBERA™ (N=123)[a]			Control (N=130)[a]			
Category	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	64.0	0.62	53.0	56.0	0.16	<0.001

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]
	(18.19)	(19.77)		(19.11)	(20.87)		
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.

Quality of life was also measured using the Impact of Weight on Quality of Life-Lite (IWQOL-Lite), which consists of 31 scale items to assess obesity-related quality of life. The total scores (where 0 is worst and 100 is best) for the ORBERA™ and control groups are summarized in Table 14. 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. The ORBERA™ group saw a significant improvement in the IWQOL-Lite.

Table 14. 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 Month 9 visit to the baseline standard deviation.
[c]P-values represent treatment group comparisons calculated using an ANOVA model.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included

15 Investigators. Among the 15 Investigators involved in the study, 9 have, by way of a signed Certification of Investigator Financial Interest Form, verified that they had no applicable financial arrangement with Allergan, the study sponsor, defined in sections 21 CFR 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

The pivotal clinical study included six (6) Investigators that had disclosable financial arrangements with Allergan, the study sponsor, disclosed under 21 CFR 54.2, not affecting the outcome of the clinical study. The nature of these disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) is detailed below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 6
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

ORBERA™ has been approved in many countries since the 1990's. As of August 31, 2014 more than 220,000 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 3,316 complaints spanning a period from January 1, 2006 to April 30, 2013 are presented in Table 15; 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 may be related to use longer than a period of 6 months.

Table 15. ORBERA™ device- and procedure- related adverse events and complaints reported through clinical product surveillance[1] between January 1, 2006 and April 30, 2013.

Events[1]	Count	Rate[2]
Difficulty with fill tube	649	0.42%
Broken device	586	0.38%
Device Deflation[3]	480	0.31%

Events[1]	Count	Rate[2]
Vomiting	337	0.22%
Pain	309	0.20%
Nausea	219	0.14%
Other	134	0.09%
Reflux	108	0.07%
Irritation/inflammation	108	0.07%
Intolerance	100	0.06%
Obstruction	46	0.03%
Infection	40	0.03%
Surgery related observation or complication[4]	30	0.02%
Dehydration	29	0.02%
Ulcer	29	0.02%
Unsatisfactory weight loss	27	0.02%
Stomach Perforation[4]	20	0.01%
Dysphagia	13	0.01%
Death[1]	12	0.01%
Unsuccessful Placement	8	0.01%
Esophageal Perforation	6	0.00%
Erosion	5	0.00%
Pancreatitis	3	0.00%
Device Displacement	3	0.00%
Necrosis[4]	3	0.00%
Hernia	2	0.00%
Device Visibility or Palpability[4]	2	0.00%
Varied injuries[4]	2	0.00%
Cardiopulmonary complication	2	0.00%
Leak(s)	2	0.00%
Allergic Reaction	1	0.00%
Myocardial Infarction	1	0.00%
Total	3,316	2.14%

Two (2) Sponsor initiated clinical trials were conducted outside the U.S., one in France (n=36 treatment subjects), and one in Australia (n=74, 37 treatment subjects and 37 controls subjects). The adverse event profile for these two (2) studies was similar to the adverse event profile seen in the U.S. pivotal study. There were no deaths and no unanticipated adverse events in either study.

A. ORBERA™ Australian Clinical 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 the ORBERA™ System 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 (31) subjects 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 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 (2) 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 (2) weeks. Two (2) subjects experienced seven (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.

B. French ORBERA™ Study

The French ORBERA™ study was a prospective, open-label, single-center post-marketing study. Forty (40) male and female subjects between 18 and 60 years of age with BMI 30 to 35 kg/m^2 with at least one obesity-related comorbidity, or BMI 35 to 40 kg/m^2 without a comorbidity were enrolled. Thirty-six (36) 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 (2) additional follow-up visits at Weeks 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 (3) serious adverse events occurred in two (2) subjects which led to removal prior to 6 months. Serious adverse events included vomiting and asthenia, ionic disorder, and vomiting with dehydration.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroeneterology and

Urology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The clinical study showed that the ORBERA™ treated subjects had a significant weight loss over the control group. The average treatment subject attained 10.2% TBWL at the time ORBERA™ is removed, compared to the 3.3% TBL attained by the control group. In addition, the study showed that much of this weight loss was maintained 3 and 6 months after ORBERA™ removal. The treatment subjects also showed significant quality of life improvement over the control group. It is should be noted that the majority of patients in the study were of Caucasian descent and females.

B. Safety Conclusions

ORBERA™ is a temporary device that offers an addition option to patients struggling with weight loss. There were a total of 14 device related SAE's and no unanticipated adverse device effects reported during the pivotal study. The procedure related SAEs were also minimal, occurring in 3 of the 160 implanted subjects. The most frequently occurring events were nausea, vomiting, pain, and gastroesophageal reflux.

The pre-clinical and clinical data establish that the ORBERA™ Intragastic Balloon System is safe for its intended use.

C. Benefit-Risks Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. As discussed above, the ORBERA™ group demonstrated statistically significant weight loss over the control group at device removal (6 months) and was able to maintain over 70% of the weight loss out to 12 months. There are risks for patients developing adverse events related to the device. Vomiting, nausea, and abdominal pain very commonly occurred in subjects following the placement of the device, although most symptoms resolve within 2 weeks. Some subjects required early device retrieval because of AE.

Additional factors to be considered in determining probable risks and benefits for the ORBERA™ device included the limited options currently available for the treatment of obesity. Although bariatric surgery is known to provide significant durable weight loss, many obese people seek less invasive interventions for weight loss. The IB-005 pivotal trial has demonstrated that the ORBERA™ can offer patients significant weight loss when used in conjunction with a diet and exercise program. The low risk profile of the pivotal study supports the safety of the device.

In conclusion, given the safety and effectiveness information presented above, the data supports the indication for use of the ORBERA™ for the treatment of morbid obesity and the probable benefits outweigh the risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The ORBERA™, intragastric balloon is a relatively low risk and moderately effective treatment for obese patients with a BMI of 30-40 kg/m^2 and is a reasonable alternative to currently available treatments. When used in conjunction with intensive diet, exercise, and behavioral modification, patients can expect clinically meaningful weight loss (i.e., 26.5 % Mean Percent Excess Weight Loss (%EWL) at 9 months (3 months after device removal). Upon removal of this device, patients should expect some degree of weight regain, but with ongoing diet, exercise, and behavior modification, some durability of weight loss is possible. Although not statistically significant, there is some improvement in obesity-associated comorbidities with the use of this device.

The overall benefits from this device, albeit limited in duration, do outweigh the potential risks.

XIV. CDRH DECISION

CDRH issued an approval order on August 5, 2015. The final conditions of approval cited in the approval order are described below.

OSB Lead PMA Post-Approval Study - ORBERA™ PAS (OPAS-001): The Office of Surveillance and Biometrics (OSB) will have the lead for this clinical study, which was initiated prior to device approval.

The OPAS-001 is a prospective, open-label, single-arm study to evaluate the safety and effectiveness of ORBERA for weight reduction in obese adults 22 years and older with a BMI of 30-40 kg/m2. This is a 52-week study in which subjects will be treated during the first 26 weeks with ORBERA in conjunction with a behavioral modification program, followed by 26 weeks of behavioral modification program alone.

A total of 284 subjects will be enrolled at 10 to 20 U.S. sites to yield 255 subjects implanted with ORBERA (assuming a 10% screen failure rate). Based on an estimated attrition rate of 10% through week 26 and 20% through week 52, the expected number of evaluable subjects is 230 subjects at 26 weeks and 204 subjects at 52 weeks. A sample size of 255 implanted subjects will provide 80% power to test the hypothesis that the rate of device- and/or procedure-related serious adverse events (SAEs) is less than 15% at 26 weeks.

A secondary study objective is to demonstrate that the mean percent Total Body Weight Loss (%TBWL) is greater than 7.5% at 26 weeks.

Other study endpoints (through 52 weeks of follow-up) include: weight loss measured by percent excess weight loss (%EWL) and percent total body weight loss (%TBL), device- and/or procedure-related adverse events, device- and/or procedure-related SAEs, gastric ulcers, esophageal injury, implant/removal procedure-related SAEs, early device explants, and balloon deflations. Subjects with gastric ulcerations at least 1.0 cm at the time of device explant will be followed with endoscopic evaluation every 8 weeks until the ulcer has visually resolved.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.