Summary of Safety and Effectiveness Data (SSED)

I. GENERAL INFORMATION

Device Generic Name: Dual Intragastric Balloon

Device Trade Name: ReShape™ Integrated Dual Balloon System

Device Procode: LTI

Applicant's Name and Address: ReShape Medical®, Inc.
100 Calle Iglesia
San Clemente, CA 92672

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P140012

Date of FDA Notice of Approval: July 28, 2015

II. INDICATIONS FOR USE

The ReShape Integrated Dual Balloon System is indicated for weight reduction when used in conjunction with diet and exercise, in obese patients with a Body Mass Index (BMI) of 30 – 40 kg/m^2 and one or more obesity-related comorbid conditions. It is indicated for use in adult patients who have failed weight reduction with diet and exercise alone.

III. CONTRAINDICATIONS

- Prior gastrointestinal surgery with sequelae (i.e. obstruction, and/or adhesive peritonitis or known abdominal adhesions).
- Prior open or laparoscopic 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 gastric mass.
- A hiatal hernia > 5 cm 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 esophageal motility disorder that may pose a safety risk

during the removal of the device.
- Severe coagulopathy.
- Hepatic insufficiency or cirrhosis.
- 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 unwilling to participate in an established medically-supervised diet and behavior modification program, with routine medical follow-up.
- Patients receiving daily prescribed treatment with aspirin, anti-inflammatory agents, anticoagulants, or other gastric irritants.
- Patients who are unable or unwilling to take prescribed proton pump inhibitor medication for the duration of the device implant.
- Patients who are known to have, or suspected to have, an allergic reaction to materials contained in the system.
- Patients who have ever developed a serotonin syndrome and are currently taking any drug known to affect the levels of serotonin in the body (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs)) should not undergo placement of the device.
- Patients who are pregnant or breast-feeding.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ReShape Integrated Dual Balloon System labeling.

V. DEVICE DESCRIPTION

The ReShape Integrated Dual Balloon System is a temporary implant designed to facilitate weight loss by occupying space in the stomach and producing a sensation of satiety. The dual balloon is delivered transorally down the esophagus and placed into the stomach using the ReShape Delivery Catheter. Once positioned, the dual balloon is inflated with a sterile saline and methylene blue solution, sealed with mineral oil, and left in the stomach for a treatment period of up to six (6) months. At the conclusion of treatment, the dual balloon is aspirated using the ReShape Removal Catheter and removed endoscopically. An illustration of the implanted dual balloon is provided in Figure 1.

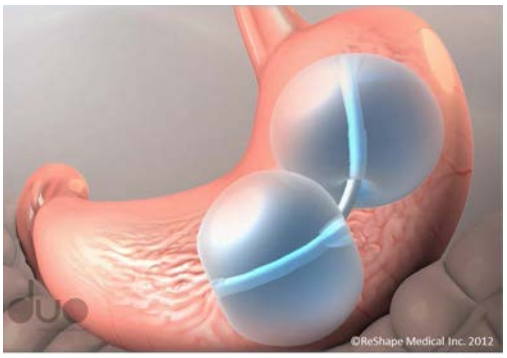


Figure 1: Implanted ReShape Integrated Dual Balloon

A. Device Components

The ReShape Integrated Dual Balloon System consists of the following components, which are packaged and supplied as individual models with separate labeling and instructions for use:

- ReShape Balloon Assembly (consisting of the dual balloon, ReShape Delivery Catheter, and accessory guidewire)
- ReShape Removal Catheter
- ReShape Valve Sealant

Additional components of the ReShape System are sterile saline solution and methylene blue.

ReShape Dual Balloon

The ReShape dual balloon consists of two (2) independently inflated, non-communicating, silicone balloons bonded to a central silicone shaft. When inflated, the dual balloon is designed to occupy a large portion of the stomach volume while conforming to the natural shape of the patient's anatomy. The device's flexible dual balloon design is intended to improve patient comfort while reducing the risk of device migration into the intestine. Each balloon can be inflated to a maximum volume of 450cc. The dual balloon is made of molded, implant grade silicone parts. The collapsed device diameter is approximately 20mm and overall length is approximately 6 inches. The dual balloon is provided to the customer sterile and pre-loaded onto a ReShape Delivery Catheter.

ReShape Delivery Catheter

The ReShape Delivery Catheter is supplied sterile, pre-loaded with a dual balloon, and packaged with a 0.035" stainless steel accessory guidewire. The delivery catheter is designed with sufficient length to be introduced transorally and extend into the patient's stomach. It includes a guidewire lumen to allow passage of the accessory guidewire. The delivery catheter is a composite of thermoplastic and stainless steel with two (2) independent fill tubes, also made with thermoplastic and stainless steel, and a thermoplastic guidewire tube which reside within the catheter shaft. The catheter shaft outer diameter is sized to be advanced down the esophagus with tolerable resistance and

with a working length that provides sufficient length for the physician to place the device into the stomach.

ReShape Removal Catheter
The ReShape Removal Catheter is a sterile, single assembly used to aspirate the saline solution from the balloon. The removal catheter is supplied separately from the dual balloon and contains independent labeling and instructions for use. The removal catheter is designed with sufficient length to be introduced endoscopically and extend into the patient's stomach. It is comprised of a thermoplastic catheter with distal sideports. The catheter is mated to a polymer valve system and manual rotational coring mechanism. The overall working length is sufficient for the physician to operate the tool outside of the patient anatomy and small enough to fit down the working channel of a 2.8mm endoscope.

ReShape Valve Sealant
The ReShape Valve Sealant is comprised of mineral oil, which is used to seal the balloon valves and prevent leaking. The ReShape Valve Sealant is supplied non-sterile in 10cc polycarbonate syringes.

B. Additional Components and Adjunct Devices

Other ReShape Integrated Dual Balloon System components and accessories not supplied by ReShape Medical, but used during the dual balloon inflation and removal procedures, include:

Sterile Saline Solution
Sterile saline solution is used to fill each balloon to the desired volume.

Methylene Blue
USP 1% methylene blue is added to the saline to provide a visual indicator to the patient (i.e., blue-green urine) when saline solution is released from a deflated balloon.

Infiltration Pump and Tubing
An infiltration pump and tubing are recommended for filling the balloon with saline.

Suction Pump and Accessories
The suction pump and accessories are used to apply suction to the ReShape Removal Catheter and aspirate the saline solution out of the dual balloon during the removal process.

Endoscopic Rat Tooth Grasping Forceps
Rat tooth grasping forceps are recommended for use during the dual balloon removal procedure to ventilate the balloons and release any residual air or fluid in the balloon following aspiration with the ReShape Removal Catheter.

Endoscopic Snare

Once both balloons are deflated, an endoscopic snare is used to capture the proximal end cap of the dual balloon and remove the balloon.

C. Principles of Operation

The ReShape Integrated Dual Balloon occupies space in the stomach for up to six (6) months. The dual balloon is placed in the stomach under endoscopic visualization during a 20-minute outpatient procedure using monitored anesthesia care (MAC) sedation.

The dual balloon is delivered transorally down the esophagus and placed into the stomach using the ReShape Delivery Catheter. Once positioned, the dual balloon is inflated with a sterile saline/methylene blue solution and remains in the stomach for a treatment period of up to six (6) months. While the dual balloon is in the stomach, and for the six (6) months after it is removed, patients work with dietitians, doctors, and nurses and receive diet and exercise counseling designed to help patients lose weight. Illustrations of the implant procedure are presented in Figure 2.

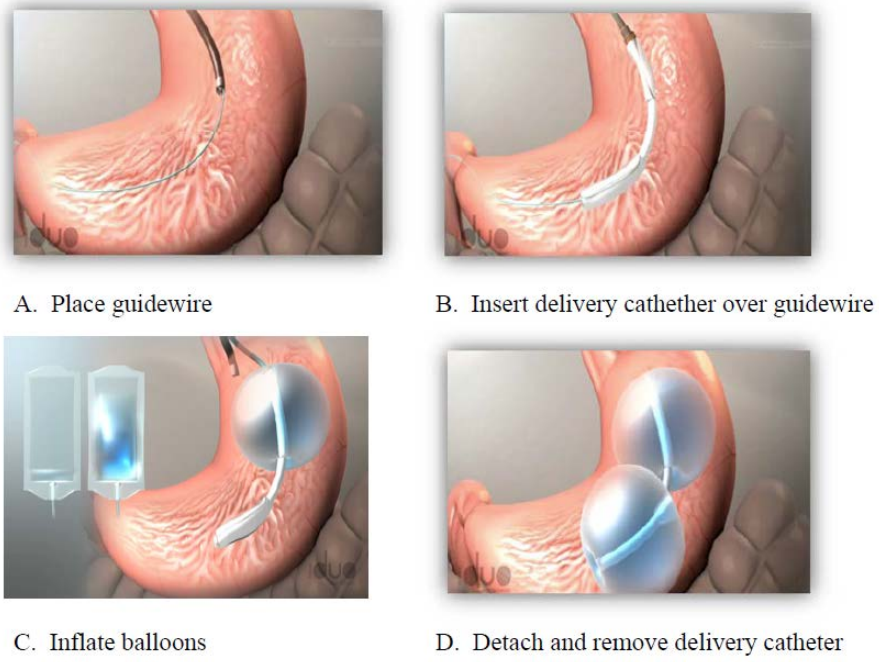
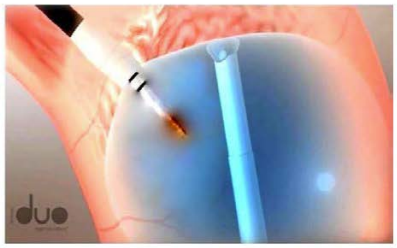
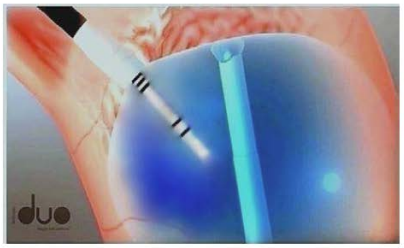


Figure 2: ReShape Integrated Dual Balloon Implant Procedure

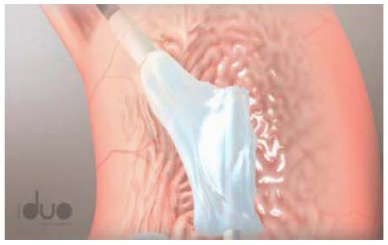
At the conclusion of treatment, the ReShape Integrated Dual Balloon is drained using the ReShape Removal Catheter and removed endoscopically. Illustrations of the removal procedure are presented in Figure 3.



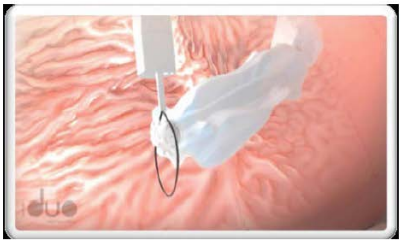
A. Puncture balloon with removal catheter cutting tip



B. Retract cutting tip and apply suction to removal catheter



C. Suction saline from both balloons



D. Grasp cap with snare and remove balloon

Figure 3: ReShape Integrated Dual Balloon Removal Procedure

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for treatment of obesity (BMI of > 30 kg/m^2), which can be divided into four (4) categories: non-surgical treatments, gastric banding, vagal blocking therapy, and obesity surgery. Some weight regain may occur with any weight reducing intervention. 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

Non-surgical treatments for obesity include:

- Diet, exercise, and behavioral modification programs; and
- Prescription weight loss medications.

B. Gastric Banding

Laparoscopic gastric banding is indicated for patients with a BMI of at least 40 kg/m^2, 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.

C. Vagal Blocking Therapy

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/m^2, 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 years.

D. Obesity Surgery

Bariatric surgery is typically recommended for patients with a BMI of at least 40 kg/m^2, or a BMI of at least 35 kg/m^2 with one or more obesity-related comorbid conditions. The most common types of bariatric surgery are described below.

Roux-en-Y Gastric Bypass
This procedure is considered to be restrictive (a small gastric pouch restricting the amount of food consumed), as well as having a malabsorptive component (bypassing some part of the intestines). In a gastric bypass, the surgeon first constructs a proximal gastric pouch and then creates an outlet from the pouch to a limb of the small bowel. This results in a bypass of most of the stomach and duodenum.

Vertical Sleeve Gastrectomy
Vertical sleeve gastrectomy is a restrictive procedure which reduces the size of the stomach by surgical removal of a large portion of the stomach. The open edges are then sutured together to form a sleeve. The size of the stomach is permanently reduced without bypassing the intestines or causing malabsorption.

Biliopancreatic Diversion Duodenal Switch
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.

VII. MARKETING HISTORY

The ReShape Integrated Dual Balloon has been CE marked in Europe since 2007. A CE mark was obtained for the ReShape Removal Catheter in 2010.

The ReShape Integrated Dual Balloon, ReShape Delivery Catheter, and ReShape Removal Catheter were approved by Health Canada in 2010.

The ReShape Integrated Dual Balloon has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that may result from use of the ReShape Integrated Dual Balloon System are both those commonly associated with gastrointestinal endoscopy procedures generally and those associated with the device specifically.

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Potential risks associated with an endoscopic procedure and sedation include adverse reaction to sedation (headache, muscle pain, nausea), anaphylaxis, cardiac arrest, death, hypoxia (low oxygen levels), myocardial infarction, esophageal perforation, infection, pneumonia, and respiratory distress. Potential adverse events for the device include gastric ulceration, esophageal perforation, significant gastric bleeding, need for blood transfusions, emergency endoscopic therapeutic intervention, abdominal pain, abdominal spasms, nausea, vomiting, bloating, belching, heartburn, dysphagia, dehydration, and sore throat.

For the specific adverse events that occurred during the REDUCE pivotal trial, see Section X, Summary of Clinical Studies below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

The integrity and performance of the ReShape Integrated Dual Balloon System was evaluated through the testing summarized in Table 1.

Table 1: Non-Clinical Performance Testing

Device Components	Test Description	Acceptance Criteria	Test Result
ReShape Dual Balloon & ReShape Delivery Catheter	Bond Integrity Test to verify bond strength between the components of the dual balloon and delivery catheter.	All device bonds must have zero leakage and meet the following pre-specified minimum tensile strength requirements to demonstrate bond integrity over the full product shelf life plus 6-month implant time: • Any device bonds under load during detachment procedure: ≥ 10 lbs • Detachment component bonds: ≥ 6 lbs • All other implant bonds: ≥ 5 lbs • All other delivery catheter bonds: ≥ 3 lbs	Pass

Device Components	Test Description	Acceptance Criteria	Test Result
	Component Integrity Test to verify the integrity of the individual components comprising the dual balloon and delivery catheter.	All device components must have zero leakage and meet the following pre-specified minimum tensile strength requirements to demonstrate component integrity over the full product shelf life plus 6-month implant time: • Any device components under load during detachment procedure: ≥ 10 lbs • All other implant components: ≥ 5 lbs • All other delivery catheter components: ≥ 3 lbs	Pass
	Detachment Force Test to verify the functionality of the detachment mechanism used to detach the inflated dual balloon from the delivery catheter during the implant procedure.	Detachment connections must meet pre-specified detachment force ≥ 1 lb and ≤ 6 lbs	Pass
	Simulated Use Test to verify the functionality and integrity of the dual balloon and delivery catheter under simulated use in an inanimate gastric model.	Device must meet the following pre-specified performance criteria associated with all delivery, inflation, and removal procedures: • System free from visual defects • Guidewire insertion and passage force ≤ 1.5 lbs • Fill tubes slide freely • Successful inflation with system free from leakage • Balloon releases without undue force • No constraint on balloon implant • Successful deflation • Balloon removal without undue force • Location markers legible and not compromised	Pass

Device Components	Test Description	Acceptance Criteria	Test Result
ReShape Dual Balloon	Implant Reliability Test to verify the reliability of the dual balloon when subjected to simulated stomach peristalsis over a six-month period.	Device must withstand 18,921,421 combined compression cycles	Pass
ReShape Removal Catheter	Bond Integrity Test to verify bond strength between the components of the ReShape Removal Catheter.	All device bonds must meet the following pre-specified minimum tensile strength requirements to demonstrate bond integrity over the full product shelf life: • Luer bond: ≥ 6 lbs • All other bonds: ≥ 10 lbs	Pass
	Component Integrity Test to verify the integrity of the individual components comprising the ReShape Removal Catheter.	Components must meet the following pre-specified minimum tensile strength requirements to demonstrate component integrity over the full product shelf life: • Tubing: ≥ 6 lbs • Wire: ≥ 10 lbs	Pass
	Electrical Safety Test to verify that the ReShape Removal Catheter does not accept or transmit electromagnetic energy from the powered suction pump, nor generate its own electromagnetic energy.	Device must meet pre-specified acceptance criteria demonstrating zero theoretical possibility for transmission, acceptance, and generation of electromagnetic energy, as well as demonstrate zero actual transmission of electromagnetic energy across all device components	Pass

Device Components	Test Description	Acceptance Criteria	Test Result
	Simulated Use Test to verify the functionality and integrity of the ReShape Removal Catheter under simulated use in an inanimate gastric model.	Device must meet the following pre-specified performance criteria associated with all usage steps: • Capable of removal from packaging • Successful delivery through endoscope without interference • Barb connector can be removed from device • Capable of indexing against implant without buckling • Capable of implant puncture and drainage • Location markers visible throughout insertion • Needle can be fully retracted after drainage • No excessive resistance during removal • No damage from suction pressure	Pass
ReShape Valve Sealant	Mechanical Integrity and Usability Test to verify that the ReShape Valve Sealant meets its design requirements for mechanical integrity and usability.	Syringe body and cap must meet the following pre-specified inspection criteria to demonstrate mechanical integrity over the full product shelf life: • Zero visual defects • Zero leaks Device must meet the following pre-specified performance criteria to demonstrate usability over the full product shelf life: • Syringe cap must be able to be manually removed from the syringe • Valve Sealant must be able to be dispensed into the device	Pass

Device Components	Test Description	Acceptance Criteria	Test Result
	Viscosity Verification Test to verify that the ReShape Valve Sealant meets its design requirement for viscosity.	Valve Sealant must have a viscosity ≥ 55cP at 37°C	Pass
ReShape Integrated Dual Balloon System	Design Validation Physician-performed test in an inanimate gastric model to validate that the clinical needs of end users have been met by the ReShape Integrated Dual Balloon System.	Device must receive a minimum physician rating of "3" on a semi-quantitative scale of 1-5 during performance of the following procedures: • Guidewire insertion • Device delivery and inflation • Device deflation and removal • Overall	Pass

B. Animal Studies

An animal study was conducted to assess the safety of the ReShape Integrated Dual Balloon System utilizing a prototype representative of the final device design. The study was conducted in compliance with Good Laboratory Practice (GLP) per 21 CFR Part 58. The animal study was conducted in a porcine model and was designed to evaluate the delivery, inflation, deflation, and removal procedures and assess the acute and chronic effects of the device.

The study used a total of 12 pigs, with device removals in three (3) pigs at 60 days, four (4) pigs at 90 days, and five (5) pigs at 180 days. The study animals were evaluated for in-life clinical observations, necropsy findings, and histopathology results. The necropsy studies were completed on stomach sections from the cardiac, fundic, and pyloric regions for each animal.

The results of the GLP animal study demonstrate that the device can be safely implanted in a healthy swine model for six (6) months with no safety concerns. There was no morbidity or mortality associated with the delivery and chronic implantation of the device. No clinical risks were identified and no significant trauma to the gastric tissue was noted.

C. Additional Studies

Biocompatibility

The ReShape Dual Balloon, ReShape Delivery Catheter, and ReShape Removal Catheter were subjected to biocompatibility testing in accordance with the requirements of ISO 10993-1:2009. All biocompatibility testing was conducted in compliance with GLP per 21 CFR Part 58.

The ReShape Dual Balloon is categorized as a mucosal membrane contacting, surface device with permanent exposure (> 30 days). The results of biocompatibility testing for the dual balloon are summarized in Table 2.

Table 2: ReShape Dual Balloon Biocompatibility Testing

Biocompatibility Test	Acceptance Criteria	Test Result
Cytotoxicity	Must meet pre-specified criteria for cytotoxicity (ISO 10993-5)	Pass
Sensitization	Must meet pre-specified criteria for sensitization (ISO 10993-10)	Pass
Irritation/Reactivity	Must meet pre-specified criteria for irritation / reactivity (ISO 10993-10)	Pass
Acute, Subacute, and Subchronic Systemic Toxicity	Must meet pre-specified criteria for acute, subacute, and subchronic systemic (ISO 10993-11)	Pass
Genotoxicity	Must meet pre-specified criteria for genotoxicity (ISO 10993-3)	Pass
Materials Mediated Pyrogenicity	Must meet pre-specified criteria for materials mediated pyrogenicity (ISO 10993-11)	Pass
Muscle Implantation	Must meet pre-specified criteria for muscle implantation (ISO 10993-6)	Pass

The above testing conducted on the Dual Balloon did not include device components that are used to fill and seal the balloon (methylene blue, sterile saline, and mineral oil). Therefore, chemical characterization testing was conducted on the device in the presence of these components. A toxicological risk assessment determined that the amounts of extracted chemical compounds are unlikely to pose significant risks of toxicological concern to patients.

The ReShape Delivery Catheter is categorized as a mucosal membrane contacting, surface device with limited exposure (≤ 24 hours). The results of biocompatibility testing for the delivery catheter are summarized in Table 3.

Table 3: ReShape Delivery Catheter Biocompatibility Testing

Biocompatibility Test	Acceptance Criteria	Test Result
Cytotoxicity	Must meet pre-specified criteria for cytotoxicity (ISO 10993-5)	Pass
Sensitization	Must meet pre-specified criteria for sensitization (ISO 10993-10)	Pass
Irritation / Reactivity	Must meet pre-specified criteria for irritation / reactivity (ISO 10993-10)	Pass
Materials Mediated Pyrogenicity	Must meet pre-specified criteria for materials mediated pyrogenicity (ISO 10993-11)	Pass

The ReShape Removal Catheter is categorized as a mucosal membrane contacting, surface device with limited exposure (≤ 24 hours). The results of biocompatibility testing for the removal catheter are summarized in Table 4.

Table 4: ReShape Removal Catheter Biocompatibility Testing

Biocompatibility Test	Acceptance Criteria	Test Result
Cytotoxicity	Must meet pre-specified criteria for cytotoxicity (ISO 10993-5)	Pass
Sensitization	Must meet pre-specified criteria for sensitization (ISO 10993-10)	Pass
Irritation / Reactivity	Must meet pre-specified criteria for irritation / reactivity (ISO 10993-10)	Pass

Sterilization, Packaging, and Shelf Life

The ReShape Dual Balloon, Delivery Catheter, and Removal Catheter are provided sterile and are intended for single use. The dual balloon and delivery catheter are supplied preassembled, fastened to a card, sealed in a Tyvek pouch, and boxed. The removal catheter is supplied separately inside a plastic coil, fastened to a card, sealed in a Tyvek pouch, and boxed. Both devices and their packaging are sterilized using gamma radiation.

Sterilization validation testing was performed in accordance with the guidelines of ISO 11137-1:2006, *Sterilization of Health Care Products – Radiation.* Validation was

conducted to demonstrate a sterility assurance level (SAL) of 10^{-6} following a gamma sterilization dose of 25 kGy.

Packaging validation testing was performed in accordance with the requirements of ISO 11607-1:2009, *Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems*. Separate packaging validations were performed for the ReShape Dual Balloon-Delivery Catheter Assembly, the ReShape Removal Catheter, and the ReShape Valve Sealant.

After accelerated aging equivalent to 12 months of shelf life (36 months for ReShape Valve Sealant) and simulated shipping conditioning, the packaging for the components was evaluated to ensure that the packaging did not leak or fail. The devices were also evaluated to determine whether the device functionality was maintained. The shelf life and packaging testing demonstrated that the packaging protects the device and the device maintains performance for a 12-month shelf life (36 months for ReShape Valve Sealant).

X. SUMMARY OF CLINICAL STUDIES

Clinical data supporting the safety and effectiveness of the ReShape Integrated Dual Balloon System are available from two (2) clinical studies, the IDE feasibility study and the IDE pivotal study. The ReShape Integrated Dual Balloon System was referred to as the "Duo" during the feasibility study and the REDUCE Pivotal Trial. The data obtained from the pivotal study, conducted under IDE G090121, constitutes the main dataset to support safety and effectiveness of the ReShape device. A summary of the studies are presented below.

Feasibility Clinical Study

The feasibility study, initiated in 2010, was a prospective, randomized, non-blinded multicenter feasibility study in which 30 subjects were enrolled and randomized in a 2:1 randomization scheme to either treatment with the ReShape Duo Balloon (Treatment Group) or to diet and exercise alone (Control Group). Treatment Subjects underwent immediate insertion of the ReShape Duo Balloon, and all subjects received diet and exercise intervention with close follow-up. The ReShape Duo device was retrieved at 24 weeks and all study subjects were followed for a total of 48 weeks. Thirty (30) subjects (21 treated and 9 control) were enrolled at three (3) study sites. Weight loss data showed that ReShape Duo Balloon treated subjects had a mean weight loss greater than that of the control subjects at every point of follow-up. All study subjects experienced at least one adverse event (AE). The most common AEs were nausea and vomiting, gastroesophageal reflux, and abdominal discomfort/pain.

Pivotal Clinical Study Design

A. Study Design

The REDUCE Pivotal Trial, was a prospective, sham-controlled, double-blinded, randomized multicenter clinical study which would enroll an initial cohort of 330 eligible obese subjects. Patients in the pivotal study were treated between August 2012 and February 2013. The database for this PMA reflected data collected through February 2014 and included 187 Treatment and 139 Control Subjects. There were eight (8) investigational sites.

Screened subjects who met inclusion and exclusion criteria, were to be randomized in a 1:1 ratio to the Treatment Group (use of the ReShape dual balloon plus a medically managed diet and exercise program) or to an active sham Control Group (to undergo an endoscopic procedure plus a medically managed diet and exercise program), to yield an estimated 300 evaluable subjects.

Following the 24 week primary effectiveness endpoint assessments, the study blind was broken. Treatment Group subjects underwent retrieval of the ReShape dual balloon at Week 24, and were seen twice-monthly for diet and exercise counseling for an additional 24 weeks, for a total follow-up of 48 weeks (19 visits total over 48 weeks). Control Group subjects who remained eligible were allowed to "crossover" to the Treatment Group and receive the ReShape dual balloon over Weeks 24 – 48 with monthly diet and exercise counseling for an additional 24 weeks, for a total follow up of 48 weeks. The ReShape dual balloon was retrieved at Week 48 from the crossover Control Group subjects and a safety visit occurred at Week 52 (21 visits total over 52 weeks). Control Group subjects who were ineligible or who declined ReShape dual balloon treatment were exited from the study after Week 24.

The study was a randomized 24-week comparison of treatment and control conditions, comparing Treatment Group mean percent excess weight loss (%EWL) to a sham-treated Control Group. The Treatment Group responder rate dichotomized at 25%EWL was also assessed. Additionally, weight maintenance during the six (6) months after device removal was evaluated for treated subjects who lost weight while the device was implanted.

The analyses for effectiveness were based on a comparison of the all subjects enrolled in and randomized to the Treatment Group or the Control Group and followed during Weeks 0 – 24 of their follow-up (Intent-to-Treat or "ITT" population). The Treatment Group was also followed after Week 24 device retrieval through Week 48 for weight loss maintenance assessments. The analysis for safety was based upon all Dual Balloon attempted subjects (for procedure-related AEs) and all Dual Balloon treated subjects (for device related AEs).

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the REDUCE pivotal study was limited to patients who met the following inclusion criteria:

1. Patients 21 to 60 years of age
2. Weight:
    a. BMI $\geq$ 30 kg/m^2 and $\leq$ 40 kg/m^2
    b. At least 5 years of obesity (with BMI $\geq$ 30)
    c. Stable weight, defined as a subject who has not gained or lost $\geq$ 5% of body weight in the 3 months preceding the screening assessment
3. Failure to lose weight, within the 36 months preceding the screening date, after participation in either of the following:
    a. A medically or commercially supervised weight loss program involving regular counseling regarding both diet and exercise
    b. Use of an FDA-approved diet drug
4. The presence of one or more obesity-related comorbid conditions
5. Willing and able to provide Informed Consent
6. Willing and able to comply with study procedures and visit schedules as specified by the protocol
7. If female, the patient must
    a. be postmenopausal for at least 1 year OR
    b. be surgically sterile, OR
    c. if of child bearing potential, must be practicing birth control, be willing to avoid pregnancy for the year of study participation, have a negative serum pregnancy test at screening, and a negative urine pregnancy test at baseline
8. Residing within a reasonable distance of the Investigator's treating office and able and willing to travel to the Investigator's office to complete all routine follow-up visits

Patients were not permitted to enroll in the REDUCE pivotal study if they met any of the following exclusion criteria:

1. History of and/or ongoing clinically significant conditions or disorders of the gastrointestinal tract (GI), including but not limited to:
    a. Prior GI surgery with sequelae, i.e. obstruction, and/or adhesive peritonitis or known abdominal adhesions
    b. Motility disorders of the esophagus and the stomach in the past 12 months, including gastroparesis or rapid gastric emptying
    c. Uncontrolled esophageal reflux symptoms
    d. Congenital or acquired GI anomalies, including atresia, stenosis, strictures, or diverticuli
    e. Inflammatory bowel disease, including Crohn's disease and ulcerative colitis
    f. Esophagitis
    g. Esophageal varices or stricture

    h. Gastric or duodenal ulceration within the last 12 months, or any history of gastrointestinal bleeding
    i. Gastrointestinal cancer
    j. Clinically significant hiatal hernia (> 3 cm)
2. Clinically significant and uncontrolled/unstable hepatic, reproductive, gastrointestinal, renal, hematologic, pulmonary, neurologic, psychiatric, respiratory, endocrine, or cardiovascular system diseases including:
    a. New York Heart Association (NYHA) Class III or IV congestive heart failure
    b. Myocardial infarction, CABG or coronary artery intervention within last 6 months
    c. Currently being treated for active coronary artery disease
    d. Transient Ischemic Attack (TIA) or stroke within last 6 months
    e. Cancer diagnosis within last 5 years (other than non-melanoma cutaneous malignancies)
    f. Parkinson's disease
3. Significant acute and/or chronic infections of any kind
4. Severe coagulopathy, hepatic insufficiency or cirrhosis
5. Uncontrolled or severe asthma, or any asthma requiring or likely to require inhaled steroid therapy during the anticipated duration of trial participation
6. Severe obstructive sleep apnea
7. Incompletely controlled hypothyroidism or hyperthyroidism
8. Severe systemic disease (consistent with an American Society of Anesthesia Physical Status Classification Score of 3 or greater)
9. Eating disorders, especially binge eating
10. Inability to walk 200 yards without assistance
11. Known allergies to any of the device materials or accessories, i.e. silicone, methylene blue, corn starch
12. Active drug or alcohol addiction within 12 months of enrollment
13. Insulin-dependent diabetes (either Type 1 or Type 2) or a significant likelihood of requiring insulin treatment in the following 12 months
14. Depressive disorder with total Beck Depression Inventory (BDI) score > 16 points, and/or BDI affective subscale score > 7 points at screening
15. Ongoing treatment, or anticipated need for such treatment, with anticoagulants, known gastric irritants such as aspirin or NSAIDs or agents that can promote gastrointestinal bleeding, within 1 month prior to enrollment, or unwillingness to forego these medications during the study period
16. Participation within 60 days of screening date in previous or ongoing clinical trial or current usage of an investigational drug or device
17. Any use of an intragastric device prior to this study
18. Genetically caused obesity, such as Prader-Willi syndrome
19. Any prior bariatric surgery or likely to undergo bariatric surgery during study follow-up period
20. Concomitant use of, or unwillingness to avoid any use of, weight loss medications, weight loss supplements, weight loss herbal preparations and/or participation in any non-study-related organized weight loss program (commercial or medical) at any

time during the study, including online or smartphone applications to track or modify food intake, exercise regimens or weight

21. Chronic opiate use (> 3 months continuous use) or likely need for opiate use during study participation
22. Contraindication or allergy to, or unwillingness to use, proton pump inhibitor medication throughout study follow-up duration
23. Pregnancy, breast feeding, or intention of becoming pregnant during the study
24. Any screening laboratory values outside of the normal range deemed clinically significant by the Investigator
25. Anemia defined as either:
    a. Hemoglobin (Hgb) value for females of < 12.0 g/dl, for males < 13.0 g/dl
    b. Abnormal red cell indices and iron deficiency
26. Smoking cessation within 3 months of study entry or plans to quit smoking during the study
27. Major surgery, open biopsy or significant traumatic injury within 3 months prior to enrollment.
28. History of significant adverse experience with sedation or anesthesia
29. Serious or uncontrolled psychiatric illness or disorder that could compromise patient understanding of or compliance with study procedures
30. Any condition that, in the opinion of the Investigator, would compromise the well-being of the patient or the study or prevent the patient from meeting or performing study requirements, including:
    a. Inability or unwillingness to sign the patient informed consent document.
    b. Inability to participate in all necessary study activities due to physical or mental limitations.
    c. Inability or unwillingness to return for all required follow-up visits.
31. Employees/family members of ReShape Medical or any of its affiliates or contractors
32. Employees/family members of the Investigator, sub-Investigators, or their medical office or practice, or surgical, bariatric or hospital organizations at which study procedures may be performed
33. An immediate family member (by marriage or blood relationship) of another subject already enrolled in the REDUCE Pivotal Trial

Presence of any of the following as determined by the Investigator before or during the Initial Endoscopy Procedure were regarded as an exclusion criterion for study participation, and subjects with these findings were immediately exited as screening failures:

1. Peptic ulcerations
2. Clinically significant hiatal hernia (> 3 cm)
3. Patulous pyloric channel
4. Erosive esophagitis
5. Varices
6. Angiectasias
7. Barrett’s esophagus

8. Esophageal stricture
9. Gastric mass
10. Any other subject characteristic that would prevent the successful insertion of a ReShape dual balloon or that in the opinion of the Investigator preclude safe use of the ReShape device

2. Follow-up Schedule

All study subjects received diet and exercise counseling consistent with the recommendations of the NIH/NHLBI document, *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (2000).* Diet and exercise counseling was administered by qualified site personnel trained by ReShape Medical. At the time of screening and enrollment, subjects were assessed and goals and treatment strategy were devised to include a 1200 cal/day dietary program. Regular review of goals, performance, and therapeutic adjustments of the diet plan occurred. The use of weight loss drugs, supplements, surgery, or participation in commercial programs was prohibited.

Tables 5 and 6 summarize the scheduled visits and patient assessments for the Treatment Group and Control Group, respectively.

Table 5: Schedule of Visits and Procedures – Treatment Subjects, Weeks 0 – 48

Visit	Screening <30 days prior to Start Date	Start Date – Day 0	7 & 14 days post initial endoscopy ± 3 days	Every 4 weeks 4 – 20 ± 2 weeks[1]	Week 24 ± 2 weeks	Every 2 weeks 26 – 46 ± 1 week[2]	Every 4 weeks 28 - 44 ± 2 weeks[3]	Week 48 ± 2 weeks or Early Termination
Informed Consent	x							
Medical History	x							
Obesity/Weight Loss History	x							
Physical Examination	x		x		x			x
Vital Signs[4]	x	x	x	x	x		x	x
Beck Depression Inventory	x							
Height without shoes	x							
Weight measure[5]	x	x		x	x		x	x
Waist and hip circumferences	x				x			x
BMI/excess weight calculation	x							
12-Lead ECG & CXR	x							
Pregnancy Test[6]	x (serum)	x (urine)						

Visit	Screening <30 days prior to Start Date	Start Date – Day 0	7 & 14 days post initial endoscopy ± 3 days	Every 4 weeks 4 – 20 ± 2 weeks[1]	Week 24 ± 2 weeks	Every 2 weeks 26 – 46 ± 1 week[2]	Every 4 weeks 28 - 44 ± 2 weeks[3]	Week 48 ± 2 weeks or Early Termination
Eligibility criteria met (3.2, 3.3)	x							
Initial Endoscopy								
Diagnostic (All Subjects)		x						
Eligibility met (3.4)		x[7]						
Randomization		x[7]						
Procedure (Treatment)		Insertion			Retrieval			
Procedure safety visit			x					
Anesthesia data		x			x			
Counseling: diet, exercise	x			x	x	x		x
Medication Assessment	x	x	x	x	x		x	x
Adverse Events		x	x	x	x		x	x

[1]That is, at Weeks 4, 8, 12, 16 and 20, all ± 2 week visit windows.
[2]That is, at Weeks 26, 28, 30, 32, 34, 36, 38, 40, 42 and 46, all ± 1 week visit windows.
[3]That is, at Weeks 28, 32, 36, 40 and 44, all ± 2 week visit windows.
[4]Vital signs: blood pressure, heart rate, temperature.
[5]Weight procedure: Subjects should wear only a patient gown and socks or stockings (or bare-feet) for all weight assessments.
[6]Pregnancy Test: Women of child-bearing potential only.
[7]Endoscopic Exclusion criteria in Section 3.4 must be met prior to randomization. If Initial Endoscopy detects an exclusionary condition under Section 3.4, the subject becomes a Screen Failure, is not finally enrolled, may not be randomized and is excluded from further study participation and analysis.

Table 6: Schedule of Visits and Procedures – Control Subjects, Weeks 0 – 24

Visit	Screening <30 days prior to Start Date	Start Date – Day 0	7 & 14 days post initial endoscopy ± 3 days	Every 4 weeks 4 – 20 ± 2 weeks[1]	Week 24 ± 2 weeks
Informed Consent	x				
Medical History	x				
Obesity/Weight Loss History	x				
Physical Examination	x		x		x
Vital Signs[2]	x	x	x	x	x
Beck Depression	x				

Visit	Screening <30 days prior to Start Date	Start Date – Day 0	7 & 14 days post initial endoscopy ± 3 days	Every 4 weeks 4 – 20 ± 2 weeks[1]	Week 24 ± 2 weeks
Inventory					
Height without shoes	x				
Weight measure[3]	x	x		x	x
Waist and hip circumferences	x				x
BMI/excess weight calculation	x				
12-Lead ECG & CXR	x				
Pregnancy Test[4]	x (serum)	x (urine)			x (urine)
Eligibility criteria met (3.2, 3.3)	x				x[5]
Initial Endoscopy					
Diagnostic (All Subjects)		x			
Eligibility met (3.4)		x			
Randomization		x[5]			
Procedure (Sham)		Sham			None
Procedure safety visit			x		
Anesthesia data		x			x
Counseling: diet, exercise	x			x	x
Medication Assessment	x	x	x	x	x
Adverse Events		x	x	x	x

[1]That is, at Weeks 4, 8, 12, 16, and 20, all ± 2 week visit windows.
[2]Vital signs: blood pressure, heart rate, temperature
[3]Weight procedure: Subjects should wear only a patient gown and socks or stockings (or bare-feet) for all weight assessments.
[4]Pregnancy Test: Women of child-bearing potential only
[5]Endoscopic Exclusion criteria in Section 3.4 must be met prior to randomization. If Initial Endoscopy detects an exclusionary condition under Section 3.4, the subject becomes a Screen Failure, is not finally enrolled, may not be randomized and is excluded from further study participation and analysis.

3. Clinical Endpoints

With regards to effectiveness, the REDUCE Pivotal Trial had two (2) co-primary effectiveness endpoints, consisting of

- An inferential test of whether the difference in the mean %EWL between the Treatment Group and Control Group at 24 weeks is significantly greater than 7.5%, and;
- An inferential test of whether the Treatment Group Responder Rate dichotomized at 25%EWL ($RESPONDER_{25\%EWL}$) at 24 weeks is significantly greater than 35%.

The secondary effectiveness endpoint for the REDUCE Pivotal Trial was an assessment of weight loss maintenance in the Treatment Group between Week 24, the time of dual balloon retrieval, and Week 48, after 24 weeks of additional diet and exercise counseling. Only those subjects with a measured and positive %EWL at 24 weeks were included in the secondary endpoint analysis. Each treatment subject was assessed for %EWL at both Weeks 24 and 48, and the ratio of Week 48 to Week 24 %EWL was calculated. Subjects with a ratio ≥ 0.40 were deemed successes, and the proportion of successes in the Treatment Group had to be significantly greater than 50% for success.

With regards to safety, the ReShape Integrated Dual Balloon System included a complete review of reported adverse events and serious adverse events, as well as device- and procedure-relatedness of adverse events. Changes in vital signs and laboratory values were evaluated, as were validated measures of symptoms of abdominal pain, nausea and vomiting. There was no pre-specified primary safety endpoint for the REDUCE Pivotal Study.

The REDUCE Pivotal Trial utilized several satisfaction and quality of life assessments to characterize subject responses to their treatment. These included:

1. The Impact of Weight on Quality of Life-Lite (IWQoL-L) was administered to all subjects at Screening, Week 24 (prior to assessment and/or endoscopy) and Week 48. IWQOL-L is a validated, 31-item, self-report measure of the obesity-specific quality of life producing a total score and five (5) domains: physical function, self-esteem, sexual life, public distress, and work.

2. The Short Form (36) Health Survey Version 2 (SF-36) was administered to all subjects at Screening, Week 24 (prior to assessment and/or endoscopy), and Week 48. The SF-36 is a validated, reliable, and responsive general assessment of self-perceived physical and mental health which scores and summarizes eight (8) clinically important Quality of Life dimensions: physical function, role limitations due to physical health, role limitations due to emotional problems, energy or fatigue, emotional well-being, social functioning, pain, and general health.

3. The Three Factor Eating Questionnaire (TFEQ-R18) was administered to all subjects at Screening and Weeks 12, 24 (prior to assessment and/or endoscopy), 36, and 48. TFEQ-R18 is a validated instrument for assessment of three (3) dimensions of human eating behavior: cognitive restraint of eating, disinhibition, and hunger.

4. The Abdominal Pain Visual Analog Scale (AP-VAS) was administered to all subjects at Screening and at Weeks 12, 24 (prior to assessment and/or endoscopy), 36 and 48. AP-VAS is a validated instrument for assessment of abdominal pain on a Likert scale.

5. The Rhodes Index of Nausea, Vomiting, and Retching (RI) was administered to all subjects at Baseline, Days 3 and 7 and at Week 4 after the Initial Endoscopy Procedures, and at Weeks 12 and 24 (prior to assessment and/or endoscopy). The RI is a validated instrument for the assessment of nausea, vomiting, and retching.

B. Patient Assessment and Accountability

Five hundred ninety-four (594) subjects were formally screened and 268 failed to meet clinical and endoscopic entry criteria. The remaining 326 subjects were randomized approximately 1:1 (187 treatment and 139 control), and 293 of these (89.9%, 167 treatment and 126 control subjects) recorded a weight at Week 24. Of these 293 at Week 24, three (3) treatment subjects were lost to follow-up and 49 control subjects declined the ReShape dual balloon treatment or were deemed ineligible at 24 weeks and did not crossover. Therefore, two hundred forty-one (241) subjects entered the 24-48 week interval, which included 164 treatment subjects and 77 crossover control subjects who were successfully implanted with a ReShape dual balloon. Two hundred (200) of the 241 continuing subjects (83.0%) recorded a weight at Week 48. At the time of database lock, 72.7% of Treatment Subjects (136/187) had completed 48 weeks of follow-up and 90.6% of Control Subjects (126/139) had completed 24 weeks of follow-up. Additionally, 77 Control Subjects were successfully implanted with the device at 24 weeks, and 83.1% of those subjects (64/77) completed an additional 24 weeks of follow-up.

A subject accountability flowchart is presented in Figure 4.

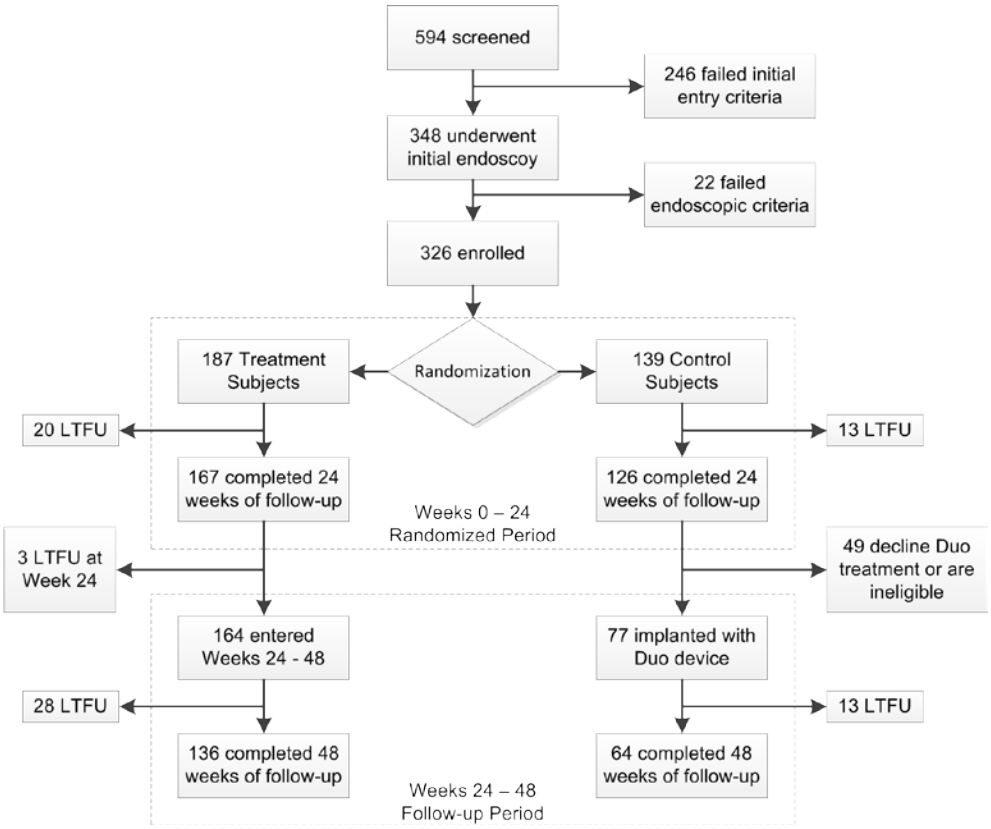


Figure 4: Subject Accountability Flowchart

C. Study Population Demographics and Baseline Parameters

Review of demographic data showed a high degree of comparability between Treatment and Control subjects in physical, medical, laboratory, and quality of life measures. Mean age was 44 years, mean BMI was 35.3, mean waist circumference was 43.3 inches, mean hip circumference was 47.2 inches, and vital signs were comparable. Table 5 presents the baseline physical characteristics for Treatment and Control Subjects.

Table 5: Baseline Physical Characteristics

Parameter	*ReShape* (N=187) Mean (SD) Median (Min, Max)	Control (N=139) Mean (SD) N Median (Min, Max)	Difference [95% CI]
Age (years)	43.77 (9.51) 43.20 (22.7, 60.6)	44.04 (10.17) 42.50 (22.1, 60.2)	0.27 [-1.89, 2.43]
Body weight (lb)	209.24 (25.84) 205.30 (154.3, 302.8)	213.21 (25.46) 215.40 (162.5, 278.9)	3.97 [-1.69, 9.63]
BMI (kg/m^2)	35.32 (2.84) 35.30 (30.1, 40.1)	35.43 (2.63) 35.50 (30.2, 40.0)	0.10 [-0.50, 0.71]

Parameter	*ReShape* (N=187) Mean (SD) Median (Min, Max)	Control (N=139) Mean (SD) N Median (Min, Max)	Difference [95% CI]
Waist circumference (in)	43.44 (4.43) 43.27 (32.5, 54.0)	43.21 (4.36) 42.99 (34.0, 53.9)	-0.23 [-1.20, 0.73]
Hip circumference (in)	47.09 (3.51) 47.01 (36.0, 55.5)	47.74 (2.88) 47.48 (41.0, 54.0)	0.65 [-0.05, 1.35]

Baseline demographic assessment showed that both treatment and control groups had 95% females with comparable rates of menopause. The demographics of the study population are typical for an obesity study performed in the US. The baseline demographics are shown in Table 6.

Table 6: Baseline Sex, Ethnicity and Race

Parameter	ReShape (N=187) % (n)	Control (N=139) % (n)
Sex (female)	95.2% (178)	95.0% (132)
Ethnicity (Hispanic/Latino)	8.0% (15)	5.8% (8)
Race:		
American Indian/Alaska Native	0.0% (0)	0.7% (1)
Asian	0.5% (1)	0.0% (0)
Black/African American	13.4% (25)	11.5% (16)
Native Hawaiian/Pacific Islander	0.0% (0)	0.0% (0)
White	81.8% (153)	85.6% (119)
Other/Refused	3.7% (7)	2.9% (4)

Study subjects in the treatment arms had comparable patterns of obesity-related comorbid conditions at the time of study entry. The most common were joint disease, hypertension, back pain, dyslipidemia, and gastroesophageal reflux disease (GERD).

D. Safety and Effectiveness Results

1. Safety Results

Safety assessment of the ReShape Integrated Dual Balloon System included a complete review of reported adverse events and serious adverse events, as well as device- and procedure-relatedness of adverse events. There was no pre-specified primary safety endpoint for the REDUCE Pivotal Study. The analysis of safety was based on the 187 Treatment Subjects randomized to receive the device and 78 control subjects who opted

to receive the device at 24 weeks (n = 265). The safety population subsets are shown in Table 7. Adverse effects are reported in tables 8 to 16.

Table 7: Safety Population Subsets

Population/Subset	Definition	Subjects
Safety Population (= ITT population)	All randomized subjects	N = 326
Treatment Subjects (Dual Balloon-treated)	Implanted Weeks 0 – 24 Followed Weeks 0 – 48	N = 187
Control Subjects	Sham controls Weeks 0 – 24, then:	N = 139
Control Subjects not opting for Dual Balloon	Exited from study through Week 24	N = 61
Dual Balloon-attempted Control Subjects	Underwent Dual Balloon procedure at Week 24	N = 78
Dual Balloon-treated Control Subjects	Implanted with Dual Balloon device at Week 24 Followed after Dual Balloon procedure Weeks 24 – 48	N = 77
All Dual Balloon-treated subjects	Implanted Treatment Subjects (N = 187) plus Dual Balloon -treated Control Subjects (N = 77)	N = 264
All Dual Balloon-attempted subjects	Same as preceding population plus one Dual Balloon -attempted Control Subject with a failed implantation procedure	N = 265

a. Serious Adverse Events

Twenty (20) subjects had a total of 31 device- or procedure-related Serious Adverse Events (SAEs). The proportion of Dual Balloon-attempted study subjects with any device or procedure-related SAE was 7.5% (20/265, 95% CI 4.2, 10.9%). There were no deaths, no device migrations out of the stomach, and no intestinal obstructions. There were 28 device-related SAEs of which 21 were vomiting, abdominal pain, epigastric pain, and nausea. The remaining 7 device-related SAEs included one ulcer-associated GI hemorrhage, one ulcer presenting with abdominal pain to the ER, one subject with abdominal pain of unclear etiology, one instance of vomiting and dehydration, and one subject with a contained esophageal perforation that resolved with hospitalization and antibiotics. There were 5 procedure-related SAEs in 5 Duo-attempted study subjects (two (2) of which were also device-related). These included one instance of esophageal tear requiring endoscopic clipping for closure of the tear, one instance of post-procedural pneumonia, the previously mentioned GI bleed related to ulcer, muscle pain requiring ER treatment after device retrieval, and the previously mentioned contained esophageal perforation. The 31

SAEs are summarized in Table 8.

Table 8: Device or Procedure-Related Serious Adverse Events

Serious Adverse Events by MedDRA Categorization	Treatment Subjects N=265			
	# of events	Subjects % (n)	Day of Onset* Mean, Median (Min, Max)	Device Removed Due to SAE # Subjects (% Subjects)
Vomiting	12	4.5% (12)	0,0 (0,0)	1/12 (8.3%)
Abdominal pain	6	2.3% (6)	20, 0 (0-118)	2/6 (33.3%)
Gastric ulcer	2	0.8% (2)	58, 58 (19-97)	2/2 (100%)
Epigastric pain	2	0.8% (2)	1,1 (0-1)	0/2 (0.0%)
Nausea	1	0.4% (1)	0	0/1 (0.0%)
Contained esophageal perforation	1	0.4% (1)	168	0/1 (0.0%)
Esophageal tear	1	0.4% (1)	9	0/1 (0.0%)
Upper gastrointestinal hemorrhage	1	0.4% (1)	17	1/1 (100%)
Epigastric discomfort	1	0.4% (1)	97	1/1 (100%)
Pneumonia	1	0.4% (1)	15	0/1 (0.0%)
Muscle pain	1	0.4% (1)	132	0/1 (0.0%)
Emesis with dehydration	1	0.4% (1)	0	0/1 (0.0%)
Dehydration	1	0.4% (1)	120	1/1 (100%)

MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event
Serious Adverse Event (SAE): any adverse event resulting in death; any adverse event which is life-threatening; any adverse event resulting in hospitalization, or significant prolongation of an existing hospitalization; any adverse event resulting in a persistent, significant impairment; any adverse event requiring significant medical or surgical intervention to prevent a significant impairment; any adverse event resulting in a congenital anomaly or birth defect

*Day of onset measured from initial procedure day

b. Adverse Events

A summary of the most common device-related adverse events is presented in Table 9.

Table 9: GI System Device-Related Adverse Events Occurring in 10% or More of Treatment Subjects

Device-Related Adverse Event (MedDRA Preferred Term)	#Subjects % Subjects (N=264)	Day of Onset	Duration (in days)	Severity Break Down # Subjects (% Subjects)	# Subjects (%Subjects) with AEs onset day ≤ Day 3 post insertion	# Subjects (% Subjects) with AEs onset day ≤ Day 3 post insertion and duration >14 days	# Subjects (% Subjects) with AEs onset day ≤ Day 3 post insertion and duration > 30 days
Vomiting	229 86.7%	Median: 0 Mean: 6.4 Range: 0-168	Median: 3 Mean: 7.3 Range: 0-84	Mild: 143/229 (62.4%) Moderate: 90/229 (39.3%) Severe: 5/229 (2.2%)	226/229 (98.7%)	24/229 (10.5%)	13/229 (5.7%)
Nausea	161 61.0%	Median: 0 Mean: 10.1 Range: 0-175	Median: 7 Mean: 24.9 Range: 0-190	Mild: 120/161 (74.5%) Moderate: 44/161 (27.3%) Severe: 1/161 (0.6%)	14/1615 (90.1%)	38/161 (23.6%)	27/161 (16.8%)
Abdominal pain	144 54.5%	Median: 1 Mean: 26.3 Range: 0-175	Median: 12 Mean: 34.8 Range: 0-194	Mild: 107/144 (74.3%) Moderate: 47/144 (32.6%) Severe: 3/144 (2.1%)	116/144 (80.6%)	48/144 (33.3%)	29/144 (20.1%)
Dyspepsia	47 17.8%	Median: 1 Mean: 24.9 Range: 0-161	Median: 15 Mean: 32.6 Range: 0-174	Mild: 41/47 (87.2%) Moderate: 6/47 (12.8%) Severe: 0/47 (0.0%)	32/47 (68.1%)	14/47 (29.8%)	5/47 (10.6%)
Eructation	44 16.7%	Median: 11.5 Mean: 34.1 Range: 0-134	Median: 90.5 Mean: 88.8 Range: 2-200	Mild: 44/44 (100.0%) Moderate: 0/44 (0.0%) Severe: 0/44 (0.0%)	17/44 (38.6%)	14/44 (31.8%)	14/44 (31.8%)
Abdominal discomfort	35 13.3%	Median: 2.5 Mean: 29.1 Range: 0-142	Median: 25 Mean: 31.6 Range: 2-115	Mild: 28/35 (80.0%) Moderate: 8/35 (22.9%) Severe: 0/35 (0.0%)	21/35 (60.0%)	8/35 (22.9%)	7/35 (20.0%)
Abdominal distension	29 11.0%	Median: 18 Mean: 41.1 Range: 0-140	Median: 29.5 Mean: 41.4 Range: 2-144	Mild: 26/29 (89.7%) Moderate: 2/29 (6.9%) Severe: 1/29 (3.4%)	8/29 (27.6%)	3/29 (10.3%)	2/29 (6.9%)
Gastric ulcer	11 10.3%*	Median: 167 Mean: 128.9 Range: 9-182	Median: 33.0 Mean: 39.9 Range: 11-81	Mild: 9/11 (81.8%) Moderate: 1/11 (9.1%) Severe: 1/11 (9.1%)	0/11 (0.0%)	NA	NA

MedDRA = Medical Dictionary for Regulatory Activities, AE = adverse event
*Ulcer rate based on N=107 subjects who received the final device design. See Table 10 for additional gastric ulcer information.

Patients self-reported severity of nausea and vomiting at multiple time points during the study using the validated Rhodes Index instrument (Table 10).

Table 10: Rhodes Index During Treatment, All ReShape-Treated Subjects

Nausea and Vomiting During Treatment Total Score 0 – 32	Day 0 N = 264	Day 3 N = 252	Week 1 N = 258	Week 4 N =239	Week 12 N =239	Week 24 N = 233
Median	0	10	3	0	0	0
Mean ± SD (Range)	0.3±1.8 (0, 16)	11.4±7.4 (0, 29)	3.9±4.5 (0, 23)	2.2±3.7 (0, 20)	0.9±2.2 (0, 15)	1.1±2.8 (0, 20)
Proportion with total score ≤ 8[1]	98.9%	41.3%	86.0%	93.3%	97.5%	97.4%

N = number, SD = standard deviation
Scale from 0 = none to 32 = severe
[1]A score of ≤ 8 approximates a mild symptom score

Patients self-reported severity of abdominal pain at multiple time points during the study using the validated Visual Analog Scale (Table 11).

Table 11: Abdominal Pain Visual Analog Scale During Treatment, All ReShape-Treated Subjects

Abdominal Pain During Treatment Total Score 0 – 100	Day 0 N = 264	Day 3 N = 252	Week 1 N = 258	Week 4 N =239	Week 12 N =239	Week 24 N = 233
Median	0	30	10	0	0	0
Mean ± SD (Range)	0.4±2.2 (0, 20)	34.1±25.7 (0, 100)	14.9±19.0 (0, 90)	6.4±11.5 (0, 65)	3.9±10.5 (0, 80)	6.0±14.4 (0, 90)
Proportion with total score ≤ 25[1]	100.0%	44.3%	78.3%	92.5%	95.4%	90.6%

VAS = visual analog scale, N = number, SD = standard deviation
Scale 0 = none to 100 = severe
[1]A score of ≤ 25 approximates a mild symptom score

The requirement for narcotic medications or injectable anti-emetic medications was not evaluated during the REDUCE Pivotal Trial.

Gastric ulceration occurred in 35% of ReShape-treated subjects during the REDUCE Pivotal Trial. The ulcerations were generally without complications, such as overt bleeding, except for one subject who had a GI hemorrhage requiring transfusion.

During the REDUCE Pivotal Trial, the ReShape device underwent a minor modification to make the device more atraumatic. This modified device was used to treat a total of 107 subjects and the rate of ulcers was substantially reduced to 10% as shown in Table 12. The 107 subjects consisted of 39 of the 77 crossover control subjects and 68 subjects from a separate, single arm study designed to assess the ulcer rate of the modified device.

Table 12: Rates of Gastric Ulceration by ReShape Device Design

Ulcer Rate	Original Design Dual Balloon Subjects Mean (n) (95% CI)	Modified Design Dual Balloon Subjects Mean (n) (95% CI)
N	225	107
% (n) 95% CI	39.6% (89) (33.2, 45.9%)	10.3% (11) (4.5, 16.0%)
Difference (95% CI) [1]	-29.3% (-37.9, -20.7%)	
p value [1]	< 0.0001	

n = number of subjects meeting condition, N = total number of subjects, CI = confidence interval

[1] p value and 95% CI calculated by chi square with continuity correction

A summary of all device-related adverse events is presented in Table 13 and the severity breakdown is provided in Table 14. A summary of all procedure-related adverse events is provided in Table 15 and the severity breakdown is provided in Table 16.

Table 13: Device-Related Adverse Events by MedDRA Categorization, All *ReShape*-Treated Subjects, During Dual Balloon Exposure

Device-Related* Adverse Events MedDRA Categorization	*ReShape* Treated Subjects N=264	
	# of events	Subjects % (n)
Subject with any device-related adverse	1042	99.2% (262)
Gastrointestinal disorders		
Vomiting	259	86.7% (229)
Nausea	183	61.0% (161)
Abdominal pain	178	54.5% (144)
Gastric ulcer	94	35.2% (93)
Dyspepsia	49	17.8% (47)
Eructation	46	16.7% (44)
Abdominal discomfort	38	13.3% (35)
Abdominal distension	30	11.0% (29)
Gastritis erosive	24	9.1% (24)
Gastroesophageal reflux disease	20	6.8% (18)
Constipation	14	5.3% (14)
Diarrhea	9	3.0% (8)

Device-Related* Adverse Events MedDRA Categorization	*ReShape* Treated Subjects N=264	
	# of events	Subjects % (n)
Abdominal rigidity	8	2.3% (6)
Gastritis	4	1.5% (4)
Esophageal injury	4	1.1% (3)
Retching	3	1.1% (3)
Abdominal tenderness	2	0.8% (2)
Gastric hemorrhage	2	0.8% (2)
Epigastric discomfort	2	0.8% (2)
Gastric mucosa erythema	2	0.8% (2)
Abdominal pain upper	1	0.4% (1)
Abnormal feces	1	0.4% (1)
Change of bowel habit	1	0.4% (1)
Dysphagia	1	0.4% (1)
Feces hard	1	0.4% (1)
Flatulence	1	0.4% (1)
Obstruction gastric	1	0.4% (1)
Esophageal pain	1	0.4% (1)
Esophageal perforation	1	0.4% (1)
Esophagitis	1	0.4% (1)
Upper gastrointestinal hemorrhage	1	0.4% (1)
Gastrointestinal injury	1	0.4% (1)
Regurgitation	1	0.4% (1)
Metabolism and nutrition disorders		
Dehydration	4	1.5% (4)
Fluid intake reduced	4	1.5% (4)
Hypophagia	4	1.5% (4)
Decreased appetite	3	1.1% (3)
Hypokalemia	2	0.8% (2)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	8	3.0% (8)
Hiccups	3	1.1% (3)
Hypoxia	1	0.4% (1)
Upper-airway cough syndrome	1	0.4% (1)

Device-Related* Adverse Events MedDRA Categorization	*ReShape* Treated Subjects N=264	
	# of events	Subjects % (n)
General disorders and administration site conditions		
Asthenia	5	1.9% (5)
Fatigue	1	0.4% (1)
Mucosal inflammation	1	0.4% (1)
Mucosal erosion	1	0.4% (1)
Non-cardiac chest pain	1	0.4% (1)
Nervous system disorders		
Dizziness	5	1.9% (5)
Headache	3	1.1% (3)
Dysgeusia	1	0.4% (1)
Other Conditions		
Back pain	3	1.1% (3)
Insomnia	2	0.8% (2)
Psychological factor affecting medical	1	0.4% (1)
Anemia	1	0.4% (1)
Conjunctival hemorrhage	1	0.4% (1)
Pharyngeal injury	1	0.4% (1)
Blood potassium decreased	1	0.4% (1)

N, n = number, MedDRA = Medical Dictionary for Regulatory Activities

*This table presents device-related adverse events only. Procedure-related adverse events are presented in Table 15. An analysis of overlapping device- and procedure-related adverse events was not performed.

Table 14: Severity Rating, Device-Related Adverse Events, All ReShape-Treated Subjects, During Dual Balloon Exposure

Device-Related Adverse Events Severity Rating*	Device-Related AEs % (n) N=1,042 total AEs
Asymptomatic	2.4% (25)
Mild	72.4% (754)
Moderate	23.8% (248)
Severe	1.4% (15)

N, n = number, AE = adverse event

*Asymptomatic = An adverse event that is not noticed by the subject and does not require

additional therapy; Mild = An adverse event that is noticeable to the subject and may require additional therapy; Moderate = An adverse event that interferes with the subject's activities and requires intervention or additional therapies; Severe = An adverse event that is intolerable, or necessitates additional therapy or places the subject at immediate risk of harm.

Table 15 - All Procedure-Related* Adverse Events by MedDRA Categorization, All Dual Balloon-Attempted Subjects, During Dual Balloon Exposure

	Dual Balloon-Attempted Subjects (N=265)	
Procedure-Related Adverse Events by MedDRA Categorization	**# of events**	**Subjects % (n)**
Total	183	42.3% (112)
Gastrointestinal disorders		
Vomiting	57	20.4% (54)
Nausea	26	9.8% (26)
Abdominal pain	12	4.5% (12)
Constipation	6	2.3% (6)
Esophageal injury	6	1.9% (5)
Abdominal distension	5	1.9% (5)
Gastroesophageal reflux disease	3	1.1% (3)
Eructation	3	1.1% (3)
Gastric hemorrhage	2	0.8% (2)
Gastrointestinal injury	2	0.8% (2)
Abdominal discomfort	1	0.4% (1)
Abdominal rigidity	1	0.4% (1)
Diarrhea	1	0.4% (1)
Dyspepsia	1	0.4% (1)
Esophageal perforation	1	0.4% (1)
Upper gastrointestinal hemorrhage	1	0.4% (1)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	30	10.2% (27)
Hypoxia	6	2.3% (6)
Cough	1	0.4% (1)
Dyspnea	1	0.4% (1)
Hiccups	1	0.4% (1)
Productive cough	1	0.4% (1)

Upper airway obstruction	1	0.4% (1)
Nervous system disorders		
Headache	2	0.8% (2)
General disorders and administration site conditions		
Chest discomfort	1	0.4% (1)
Mucosal erosion	1	0.4% (1)
Mucosal hemorrhage	1	0.4% (1)
Injury, poisoning and procedural complications		
Procedural complication	2	0.8% (2)
Pharyngeal injury	1	0.4% (1)
Other conditions		
Myalgia	2	0.8% (2)
Vertigo	1	0.4% (1)
Conjunctival hemorrhage	1	0.4% (1)
Pneumonia	1	0.4% (1)
Blood potassium decreased	1	0.4% (1)

N, n = number, MedDRA = Medical Dictionary for Regulatory Activities

*This table presents procedure-related adverse events only. Device-related adverse events are presented in Table 13. An analysis of overlapping device- and procedure-related adverse events was not performed.

Table 16 - Severity Rating, Procedure-Related Adverse Events, All Dual Balloon-Attempted Subjects, During Dual Balloon Exposure

Procedure-Related Adverse Events Severity Rating*	**Procedure-Related AEs % (n) N=183 total AEs**
Asymptomatic	4.9% (9)
Mild	85.8% (157)
Moderate	6.6% (12)
Severe	2.7% (5)

N, n = number, AE = adverse event

*Asymptomatic = An adverse event that is not noticed by the subject and does not require additional therapy; Mild = An adverse event that is noticeable to the subject and may require additional therapy; Moderate = An adverse event that interferes with the subject's activities and requires intervention or additional therapies; Severe = An adverse event that is intolerable, or necessitates additional therapy or places the subject at immediate risk of harm.

c. Device Failures and Replacements

A total of 265 insertion procedures were performed in the REDUCE Pivotal Trial. These consisted of 187 subjects initially randomized to the Treatment Group, plus an additional 78 subjects initially randomized to the Control Group who elected to receive a ReShape dual balloon after completion of the Week 24 follow-up visit.

The insertion procedure had a high degree of success, with 99.6% (264/265) of procedures resulting in successful implantation of the dual balloon. The mean ReShape Dual Balloon insertion time was 8 minutes (median 7, range 3-24 minutes), and operators rated all aspects of the procedure as easy. The retrieval procedure had a success rate of 100%. The average endoscopic retrieval time took 14 minutes (median 11, range 4 to 120 minutes).

Sixteen (6.1%) of 264 successfully implanted dual balloons were found to have a balloon deflated at the time of retrieval. Blue-green urine was reported by the subject in 11/16 (69%) instances which occurred on average after 118 days (median 120, range 67-167 days). Unrecognized deflations occurred in 5/16 (31%) instances, which were found at routine 24 week retrieval. No device migrated out of the stomach at any time during the study.

2. Effectiveness Results

a. Primary Endpoint Outcome

The analysis of effectiveness was based on the 187 Intent-to-Treat Treatment Subjects at 24 weeks. Key effectiveness outcomes are presented in Tables 17 and 18.

The REDUCE Pivotal Trial met its first co-primary effectiveness endpoint. The intent-to-treat mean %EWL for Control Subjects at 24 weeks was 11.3% and for the Treatment Subjects was 25.1%, giving a mean difference in %EWL of 13.9%. The p-value for the superiority test for a 7.5% superiority margin was 0.0041, demonstrating that the ReShape-treated subjects had a weight loss significantly greater than that for Control Subjects plus a superiority margin of 7.5%EWL, as seen in Table 17.

Table 17: Primary Effectiveness Endpoint #1 – Comparison of Mean %EWL

Primary Endpoint #1 %EWL at 24 Weeks	ReShape Dual Balloon	Sham Control	Difference (95% CI)	p value[2]
	Mean (SE) (95% CI) [1]	Mean (SE) (95% CI) [1]		
Intent-to-Treat Population	25.08% (1.596) (21.95, 28.21%)	11.29% (1.881) (7.61, 14.98%)	13.91% (9.14, 18.67%)	0.0041

[1]Estimated mean and standard error from combining estimates across 10 imputed datasets by the method of Rubin (1987).

[2]Difference between groups, confidence limits and p-value from one-sided t-test all calculated by combining difference between groups across 10 imputed datasets and adjusted for gender and BMI by the method of Rubin (1987). P-value calculated accounting for a 7.5% lower limit.

The REDUCE Pivotal Trial met its second co-primary effectiveness endpoint. The intent-to-treat proportion of ReShape-treated subjects who achieved a 25%EWL or greater weight loss at 24 weeks was 48.8%, with a lower confidence bound of 41.6%, which was significantly greater than the required responder rate of 35% ($p < 0.0001$), as seen in Table 18.

Table 18: Primary Effectiveness Endpoint #2 – Treatment Group Responder Rate

Primary Endpoint #2: Proportion of Treatment Subjects with %EWL ≥ 25	ReShape Dual Balloon %	95% CI	p value [2]
Intent-to-Treat Population [1]	48.8%	(41.6, 56.0%)	< 0.0001

[1] Estimated proportion from combining estimates across 10 imputed datasets by the method of Rubin (1987).

[2] Normal one-sided t-test from combining estimates across 10 imputed datasets by the method of Rubin (1987) compared against the null of 35%.

b. <u>Secondary Endpoint Outcome</u>

The secondary endpoint evaluated weight maintenance on 156 of the 187 treated subjects with a measured and positive %EWL at 24 weeks. The secondary endpoint evaluating weight maintenance was not met as more than 50% of Treatment Subjects who lost weight with the device did not maintain greater than 40% of their %EWL for the 24 weeks after the device was removed. The proportion of subjects with a Week 48 %EWL value that was 40% or greater than the Week 24 %EWL responder rate was 49.4% which was not significantly greater than 50% ($p = 0.377$), as seen in Table 19.

Table 19: Secondary Endpoint – Treatment Group Weight Loss Maintenance

Secondary Endpoint: Proportion of Treatment Subjects with %EWL Week 48 / %EWL Week 24 ≥ 0.40	ReShape Dual Balloon %	95% CI	p value [2]
Intent-to-Treat Population [1*]	49.4%	(41.2, 57.5%)	0.5610

[1] Estimated proportion from combining estimates across 10 imputed datasets by the method of Rubin (1987).

[2] Normal one-sided t-test from combining estimates across 10 imputed datasets by the method of Rubin (1987) compared against the null of 50%.

[*] 156 of 187 treatment subjects demonstrated a measured and positive %EWL at 24 weeks and were included in the secondary endpoint analysis.

The average Treatment subject with weight loss at Week 24 maintained 60% of this weight loss through 48 weeks of follow-up. The weight loss maintenance outcomes (for subjects who lost weight with the device) are presented in Table 20.

Table 20: Distribution of Weight Loss Maintenance in Week 48 Completed Subjects[1]

Responder status	Ratio of Week 48 %EWL to Week 24 %EWL	Total	%
Non-responder	< 0 (gained more weight than lost)	26	20.6%
	0 - < 0.4 (regained more than 60% of lost)	31	24.6%
Responder	0.4 - < 1.00 (regained less than 60% of lost)	38	30.2%
	≥ 1.00 (continued to lose weight after balloon)	31	24.6%
	Total	126	100.0%

[1] Completed subjects are defined as having a measured and positive %EWL at 24 weeks and a measured %EWL at 48 weeks. 126 of the 156 Intent-to-Treat subjects evaluated in the secondary endpoint had a measured %EWL at 48 weeks and were therefore completed subjects. 30 of 156 Intent-to-Treat subjects evaluated in the secondary endpoint were lost to follow-up between week 24 and week 48.

c. Additional Analyses

Table 21: Weight Loss Parameters at 24 and 48 Weeks by Treatment Group

	ReShape Subjects				Control Subjects[1]				
Analysis Group	N	%EWL Mean (SD) (Min, Max)	%TBL Mean (SD) (Min, Max)	Pounds Mean (SD) (Min, Max)	N	%EWL Mean (SD) (Min, Max)	%TBL Mean (SD) (Min, Max)	Pounds Mean (SD) (Min, Max)	%EWL p-value[2]
Intent-to-Treat at 24 weeks*	187	25.1%	6.8%	14.3	139	11.3%	3.3%	7.2	0.0041
Per Protocol at 24 weeks**	148	28.5%(20) (-16.9,130.7)	7.8%(5.4) (-6.3,24.7)	16.4(11.7) (-14.6,54.6)	120	13.4%(22.1) (-25.1,102.9)	3.9%(6.2) (-6.7,33.6)	8.5(14.1) (-14.1,86.8)	0.0017

Analysis Group	*ReShape* Subjects				Control Subjects[1]				
	N	%EWL Mean (SD) (Min, Max)	%TBL Mean (SD) (Min, Max)	Pounds Mean (SD) (Min, Max)	N	%EWL Mean (SD) (Min, Max)	%TBL Mean (SD) (Min, Max)	Pounds Mean (SD) (Min, Max)	%EWL p-value[2]
Intent-to-Treat at 48 weeks***	156	18.2%	4.8%	9.9		NA	NA	NA	NA
Per Protocol at 48 weeks****	86	21.5%(29.1) (-36.9,121.0)	5.6%(7.5) (-7.2,28.9)	11.6(15.7) (-17.2,64.5)		NA	NA	NA	NA

[1]Control subjects weight loss parameters were not assessed at 48 weeks

[2]ITT group: One-sided t-test from combining difference between groups across 10 imputed datasets by the method of Rubin (1987) adjusted for gender and BMI. %EWL comparison accounts for a 7.5% lower limit. Per Protocol group: One-sided analysis of covariance adjusted for gender and BMI. %EWL comparison accounts for a 7.5% lower limit.

*Imputation technique does not allow computation of standard deviation or minima/maxima

**Completed 24 weeks of study follow-up and attended at least 75% of scheduled follow-up visits. In addition Treatment Group subjects had the device in place for at least 20 of the 24 weeks.

***Analysis includes 156 of 187 treatment subjects with a measured and positive %EWL at 24 weeks. Imputation technique does not allow computation of standard deviation or minima/maxima.

****Analysis includes 86 of 187 treatment subjects with a measured and positive %EWL at 24 weeks who completed 48 weeks of study follow-up and attended at least 75% of scheduled follow-up visits.

The study was not powered for assessment of changes and did not include a pre-determined endpoint for factors associated with health improvements; however, data were collected to measure changes in comorbid conditions and quality of life. Results suggest that there were small, but not meaningful, improvements in comorbid parameters for diabetes, hypertension, and hyperlipidemia from baseline to 24 weeks in the treatment group, but these small improvements were not significantly different from the improvements seen in the control group. These changes from baseline generally persisted through 48 weeks for the treated subjects (the control subjects were not evaluated after 24 weeks for comparison). Statistically significant differences were seen in waist (0.94 inches) and hip circumference (0.62 inches) of treated subjects compared to control subjects at 24 weeks.

Results also showed a statistically significant improvement in quality of life measures (IWQoL-Lite Total and SF-36: physical functioning) at 24 weeks in the treated subjects as compared to the control subjects; these improvements generally persisted in the treated subjects to 48 weeks. No differences were seen in other categories of the SF-36 survey or the Three Factor Eating Questionnaire (TFEQ).

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

eight (8) principal investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology 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.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The REDUCE pivotal study had two (2) co-primary effectiveness endpoints, both which were met and demonstrated that the ReShape dual balloon treatment was more effective than a medically supervised diet and exercise program alone for 24 weeks.

The first co-primary endpoint specified that Treatment Group would achieve a mean percent excess weight loss (%EWL) that was significantly greater than the Control Group by a superiority margin of 7.5 at 24 weeks when the device was removed. The average %EWL at 24 weeks was 25.1% for the Treatment Group and 11.3% for the Control Group, resulting in an average difference between the Treatment and Control Group of 13.9% (95% CI: [9.1, 18.7%]).

The second co-primary endpoint specified that significantly greater than 35% of subjects in the Treatment Group would achieve greater than 25% EWL at 24 weeks when the device was removed. The study demonstrated that 48.8% (95% CI: [41.6, 56.0%]) of subjects in the Treatment Group had achieved 25% EWL.

The study also investigated a secondary effectiveness endpoint which evaluated weight maintenance for 24 weeks after device removal in the Treatment Group in subjects who lost weight with the device (those that gained weight or had an %EWL equivalent to zero were not included in the analysis). The secondary endpoint was not met. This endpoint specified that significantly greater than 50% of subjects in the Treatment Group would maintain 40% of their excess weight loss (the ratio of Week 48 %EWL/Week 24 %EWL was greater than 0.4). The results demonstrate that 49.4% (95% CI: [41.2, 57.5%]) of subjects in the Treatment Group maintained 40% of their excess weight loss. The results showed that subjects who lost weight with the device maintained an average of 60% of the lost weight over an additional 24 weeks of observation following dual balloon retrieval. Furthermore, that 24.6% of subjects continued to lose weight, and 20.6% of subjects gained more weight than was lost after the device was removed.

Study results suggested small, but not meaningful, improvements in comorbid conditions for diabetes, hypertension, and hyperlipidemia from baseline to 24 weeks in the Treatment Group. These small improvements were not significantly different from the improvements seen in the Control Group and may have been attributable to weight management alone, and not specifically treatment with the dual balloon.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above.

The REDUCE pivotal study did not have a pre-specified safety endpoint. The safety assessment of the ReShape Integrated Dual Balloon System included a complete review of reported serious adverse events and adverse events, as well as device- and procedure-relatedness of adverse events.

There were no unanticipated adverse device effects, no deaths, no intestinal obstructions, and no gastric perforations that occurred in the pivotal study. Procedural risk was consistent with low-risk endoscopic interventions.

There were 31 SAEs that occurred among 20 subjects resulting in a device- or procedure-related SAE rate of 7.5% (20/265). A significant portion of the Treatment subjects experienced nausea, vomiting, and abdominal pain; most AEs following the placement of the device resolved within 30 days. Thirty-nine (39) subjects required early device removal due to an adverse event (39/264 or 14.8%).

The most significant concern is regarding the development of gastric ulcerations and the potential for gastric bleeding. In the study one subject had an ulcer-related GI hemorrhage and all ulcers in subjects completing follow-up resolved clinically with PPI therapy after device removal, but resolution was not confirmed by endoscopy. Although the gastric ulceration rate was significantly reduced by a minor design modification to the device, there does not appear to be any specific symptoms that are able to distinguish subjects with gastric ulcerations.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in clinical studies conducted to support PMA approval as described above, and is based on a demonstration of moderate weight loss with the device and some weight lost maintenance in some subjects 24 weeks after the device was removed. However, there was only a marginal benefit of weight loss among subjects in the Treatment Group as compared to those in the Control Group. 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 30 days. Some subjects required early device retrieval because of an AE. The most worrisome risk related to the use of the device is the development of gastric ulcerations.

Additionally, there are no predictors or specific indicators to identify patients with gastric ulcerations and provide early intervention or prophylactic device removals.

Additional factors to be considered in determining probable risks and benefits for the ReShape Integrated Dual Balloon System device included the limited options currently available for the treatment of obesity. The effectiveness for the dual balloon is better than what would be expected with diet and exercise or pharmacologic therapy; however, the effectiveness is substantially less than what would be expected with gastric banding or other surgical interventions. The dual balloon has the potential for moderate short-term weight loss with an acceptable safety profile. FDA's recommendation for Approval of the ReShape Integrated Dual Balloon System is based in part on the limited options available to patients with mild to moderate obesity who have failed other means for conservative weight loss.

In conclusion, given the available information above, the data supports the intended use of the ReShape Integrated Dual Balloon System for the treatment of morbid obesity and the probable benefits outweigh the probable risks.

D. Overall Conclusion

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 primary effectiveness endpoints demonstrated an overall mean %EWL of 25.1% in the Treatment Group as compared to 11.3% in the Control Group. Additionally, the finding that over 40% of subjects in the Treatment Group achieved at least 25% EWL supports that the device is likely to be clinically effective in a significant portion of patients. Finally, the adverse event profile for the ReShape Dual Integrated Balloon System is reasonable with an acceptable safety profile.

In conclusion, the benefit-risk model profile favors the approval of this device.

XII. CDRH DECISION

CDRH issued an approval order on June 28, 2015. The final conditions of approval cited in the approval order are described below.

OSB Lead PMA Post-Approval Study – REDUCE Post-Approval Study: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval.

The REDUCE PAS is a prospective, open-label, single-arm study of the ReShape Integrated Dual Balloon System (the "Dual Balloon"), for weight reduction when used in conjunction with diet and exercise. This is a 48-week study in which subjects will be treated during the first 24 weeks with ReShape Dual Balloon in conjunction with diet/exercise counseling, followed by 24 weeks of counseling alone. A total of 250 subjects will be enrolled at 10 to 15 sites in the United States; 217 evaluable subjects

will be available at 24 weeks.

The primary objective is to evaluate the safety of ReShape Dual Balloon in obese patients 22 years and older with a BMI of 30 to 40 kg/m^2 and one or more obesity-related comorbidities, and who have failed weight reduction with diet and exercise alone. Specifically, the study will evaluate the rate of device- and/or procedure-related SAEs (composite safety endpoint) through 24 weeks of treatment with ReShape Dual Balloon. The observed rate will be compared to a performance goal of 13%.

Other study endpoints include: weight loss as measured by percent excess weight loss (%EWL) and percent total body weight loss (%TBL) at 24- and 48-weeks; components of the composite safety endpoint including gastric ulcer SAEs, esophageal injury SAEs, device-related SAEs, and insertion/retrieval procedure-related SAEs; early device explants; and device deflations. Subjects with gastric ulcers 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. A subgroup analysis of these study endpoints will be performed in subjects who are 60 years and older.

In addition to the main safety assessment at 24 weeks, this study will also evaluate the durability of weight loss in at least 182 subjects at 48 weeks.

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

XIII. 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.