

FDA Executive Summary Memorandum

Prepared for the December 3, 2010, Meeting of the
Gastroenterology and Urology Devices Advisory Panel

P000008/S017

LAP-BAND[®] Adjustable Banding System
Allergan

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I. Introduction

The applicant, Allergan, Inc., has submitted a supplement to their premarket approval application (PMA) to FDA requesting approval to expand the indication for use for the LAP-BAND[®] Adjustable Gastric Banding System (LAP-BAND[®]). The device is a permanent implant placed around the upper portion of the stomach to reduce the amount of food that can be ingested resulting in reduced calorie intake and weight loss. The LAP-BAND[®] is currently approved for weight reduction for severely obese patients with a Body Mass Index (BMI) of at least 40 or a BMI of at least 35 with one or more severe comorbid conditions.

Obesity is one of the major public health issues within the United States because of its high prevalence, economic impact and its relationship with several medical conditions. Estimates for all categories of obesity; overweight (Body Mass Index (BMI) ≥ 25), obesity (BMI ≥ 30) and extreme obesity (BMI ≥ 40) have shown increasing trend, with the most pronounced increase observed in individuals with a BMI greater than 30. Individuals who are overweight generally tend to increase in weight and do not lose clinically significant amounts of weight.

The prevalence of obesity is continuing to increase in the US and worldwide. Obese patients risk for medical complications and early mortality is best defined by the BMI— a relationship between weight and height (kilograms divided by meters squared). The higher the BMI, the higher the risk for medical complications. These complications include diabetes, hypertension, hyperlipidemia, cholelithiasis, steatohepatitis, gastroesophageal reflux disease (GERD), pulmonary hypertension, obstructive sleep apnea, urinary stress incontinence, and coronary artery disease. Operative risk is also a major concern to surgeons and anesthesiologists alike when dealing with morbidly obese patients.

Obesity is the result of ingesting more energy in the form of calories than is expended. Even small excesses over short periods of time can lead to increases in body fat. Genetic and environmental factors are also believed to play a role in obesity.

The mainstay of therapy for obesity has been dietary modification – consuming fewer calories. A 500-800 kcal/day deficit and limiting fat to $< 30\%$ of total calories is considered reasonable for most patients. In addition to dietary changes, behavioral modifications are often employed. This includes increased physical activity (80 minutes of moderate-intensity activity per day), especially aerobic exercise.

Pharmacotherapy is often employed in those patients who do not respond to dietary and lifestyle modifications. Its effects are better when used in conjunction with behavior modification. Several drugs are FDA–approved for the treatment of obesity. Unfortunately drugs are a short-term treatment – patients usually regain weight when the drug is discontinued and the effectiveness of the drug may diminish with time.

Conventional forms of weight loss intervention; lifestyle and behavioral modification, calorie-restricted diets, and pharmacotherapy can be effective, however, they often result in insufficient weight loss and any weight loss is rarely sustained over a long period of time.

Surgery has been the most effective therapy for morbid obesity, especially those with BMI ≥ 40 . Several restrictive procedures have evolved including gastric stapling and vertical-banded

gastroplasty. These essentially create a smaller gastric pouch, thereby limiting calorie intake. The other common surgical procedures are bypass operations such as the Roux-en-Y gastric bypass or biliopancreatic bypass. This creates a small gastric pouch, but can also create “dumping syndrome”. This may be complicated by malabsorption of minerals or elements such as iron, calcium, and vitamin B12. The latter may also cause nutritional deficiencies because of fat and fat-soluble vitamin malabsorption. These surgical procedures may eliminate 40-70% of excess weight. Recently vertical gastroplasty has been performed with good results for the same patient populations.

The emergence of adjustable gastric banding devices has stemmed from the desire to perform effective, efficient, safe, and minimally-invasive obesity surgery. Banding is a restrictive-type procedure in which an expandable ring is placed around the stomach. It may be expanded or deflated post-operatively by adding or removing saline from a subcutaneously implanted access port. This in effect controls the size of the gastric pouch and directly affects satiety. The LAP-BAND[®] System is approved in the United States for weight loss in severely obese adults. LAP-BAND[®] design, surgical implantation methods, and postoperative use (adjustment) of the device utilized for the subjects implanted in this study is the same as the currently approved device.

The sponsor has and is continuing to conduct a multicenter, prospective, non-randomized, observational clinical study of the safety and effectiveness of the LAP-BAND[®] System for weight loss in patients with a BMI between 30 and 40 kg/m² under G070039. The PMA supplement (S017) under review includes the clinical study summary report, a literature review; draft modified labeling specific to lower BMI patients, and postmarket approval data collection plans.

Current recommendations, from the National Institutes of Health (NIH) and several other professional organizations,^{1,2,3,4} for patients that should be considered for bariatric surgery do not include patients with a BMI of less than 40 kg/m² unless the patient has a serious comorbid condition. Patients with a BMI of less than 35 kg/m² (even with a comorbid condition) are usually not considered appropriate for bariatric surgery. Expansion of the indication to include lower BMI patients would change the current practice of medicine with respect to bariatric surgery.

¹ Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight And Obesity in Adults
http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm

² Guidelines for Clinical Application of Laparoscopic Bariatric Surgery
www.sages.org/publication/id/30/

³ Bariatric Surgery: The American Society for Metabolic and Bariatric Surgery Guidelines
www.lapsurgery.com/BARIATRIC%20SURGERY/ASBS.htm

⁴ American Association of Clinical Endocrinologists, the Obesity Society and American Society for Metabolic & Bariatric Surgery Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient
<http://www.aace.com/pub/pdf/guidelines/Bariatric.pdf>

II. Regulatory History

The PMA supplement, P000008/S017, has been reviewed by the Office of Device Evaluation, Division of Reproductive, Gastro-Renal and Urological Devices within the Center for Devices and Radiological Health of the Food and Drug Administration. A chronology of the key milestones with respect to this premarket approval application (PMA) application is provided below.

- **June 5, 2001** – FDA approval of PMA P000008 with the LAP-BAND[®] indicated for use in severely obese patients with a Body Mass Index (BMI) of at least 40 or a BMI of at least 35 with one or more severe comorbid conditions.
- **April 24, 2010** – FDA filed supplement 17 to P000008 for the LAP-BAND[®] device. The submission contained the analysis of the 12 month data for the lower BMI patients enrolled in the pivotal study.
- **July 21, 2010** – FDA requested (via email) that the sponsor provide additional information regarding the statistical analysis and the Post Approval Study.
- **August 12, 2010** – Sponsor provided an update to the FDA including weight loss information at the 24 month time point, an update on adverse events, and new information available since the original submission.
- **September 24, 2010** – Sponsor submitted a response to FDA’s July 21, 2010 email regarding questions on the statistical analysis and the Post Approval Study. The sponsor also provided a draft Summary of Safety and Effectiveness.

III. Proposed Indications for Use

The LAP-BAND[®] was approved on June 5, 2001 for “use in weight reduction for severely obese patients with a Body Mass Index (BMI) of at least 40 or a BMI of at least 35 with one or more severe comorbid conditions, or those who are 100 lbs or more over their estimated ideal weight according to the 1983 Metropolitan life Insurance Tables (use the midpoint for medium frame). It is indicated for use only in severely obese adult patients who have failed more conservative weight-reduction alternatives, such as supervised diet, exercise and behavior modification programs. Patients who elect to have this surgery must make the commitment to accept significant changes in their eating habits for the rest of their lives.”

The proposed expanded Indication for Use for the LAP-BAND[®] is:

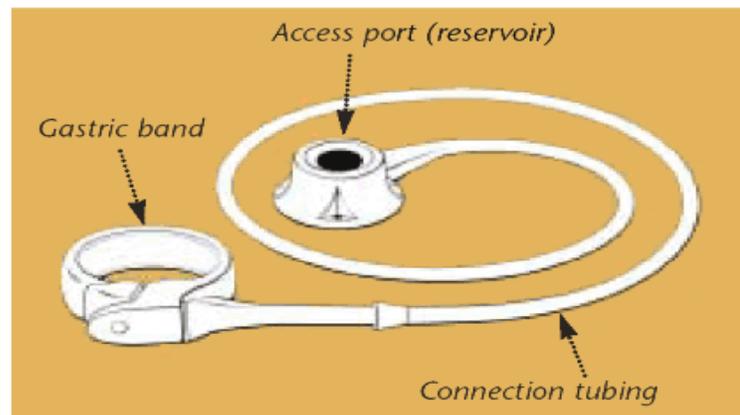
“The LAP-BAND[®] System is indicated for use in weight reduction for obese patients with a Body Mass Index (BMI) of at least 35kg/m² or a BMI of at least 30 kg/m² with one or more comorbid conditions.

It is indicated for use in obese adult patients who have failed more conservative weight reduction alternatives, such as supervised diet, exercise and behavior modification programs. Patients who elect to have this surgery must make the commitment to accept significant changes in their eating habits for the rest of their lives.”

IV. Device Description

The LAP-BAND[®] System is a long-term implantable adjustable gastric band intended to induce weight loss in obese patients by limiting food consumption (restrictive rather than malabsorption). The LAP-BAND[®] System is surgically implanted (generally using a laparoscopic technique), to create a restricted opening (stoma) and a small gastric pouch to limit food consumption and induce early satiety. The main components of the device (Fig. 1) are the silicone band, the access port, and kink-resistant tubing used to connect the other two components. The inner surface of the silicone band, which is placed around the stomach, is inflatable and connected by the kink-resistant tubing to the access port (a remote injection site). The access port is placed in or on the rectus muscle to allow non-surgical, percutaneous adjustments to the band and thus, the stoma diameter, by adding or removing sterile saline. Five LAP-BAND[®] System models have been approved for use in the United States (Fig. 2).

Figure 1: LAP-BAND[®] Adjustable Gastric Banding System



The LAP-BAND Adjustable Gastric Banding System

Figure 2: Approved LAP-BAND® System Models

Design Features	LAP-BAND® 9.75	LAP-BAND® 10.0	LAP-BAND® VG	LAP-BAND AP® Standard	LAP-BAND AP® Large
					
	9.75	10.0	VG	APS	APL
Belt and Buckle	Not Openable	Not Openable	Not Openable	Openable Locking Mechanism	Openable Locking Mechanism
Shell	Smooth Continuous	Smooth Continuous	Smooth, Pre-grooved (Omniform®)	Smooth, Pre-grooved (Omniform®)	Smooth, Pre-grooved (Omniform®)
	325° inflation area and no cushion effect under belt and buckle	325° inflation area and no cushion effect under belt and buckle	325° inflation area and no cushion effect under belt and buckle	360° inflation area with cushion effect under belt and buckle	360° inflation area with cushion effect under belt and buckle
Fill Volume	0-4 mL	0-4 mL	0-10 mL	0-10 mL	0-14 mL
Overall LAP-BAND®	Assembled injection molded components	Assembled injection molded components	Assembled injection molded components	One-piece injection molded	One-piece injection molded

The adjustable gastric band of the LAP-BAND® System approved in 2001, in two sizes a 9.75cm and a 10.00cm inner circumference.

In December of 2003, the company received approval to expand the LAP-BAND® System line to include an 11.0cm LAP-BAND®. The 11cm design, called the VG, was a dimensional and design modification to the approved 10cm LAP-BAND® System. In addition to the increased length for the VG, the surface of the shell has pre-determined areas where the shell will fold. These pre-formed grooves allow for increased adjustability of the shell and provide even inflation around the inner circumference of the band. The maximum fill volume of the original 9.75 and 10.0 cm bands was 4 ml, while the 11cm VG has a maximum fill volume of 10cc.

In April of 2006, the company received approval to expand the LAP-BAND® System product line to add a large and small “Advanced Platform” (AP) design. This AP design is based on the VG design except that the AP has a 360° inflating balloon component. In addition, the AP design can be opened (unlocked) to allow adjustment either during the initial placement surgery or during revision surgery. Currently the AP design accounts for 99% of the LAP-BAND® Systems sold worldwide.

V. Bench Testing

The LAP-BAND® System is a legally marketed device and is the same device that was approved in the original PMA and in several PMA supplements. Since the LAP-BAND® System has not

been further modified for the new indication for use; no bench testing was required by FDA for this application.

VI. Overview of P000008 – LAP-BAND[®] Used for Obesity in Patients with BMI \geq 40

The LAP-BAND[®] Adjustable Gastric Banding System for Obesity (BMI of at least 40 or a BMI of at least 35 with one or more severe comorbid conditions, or for those who are 100 lbs or more over their estimated ideal weight (Met Life Tables)) was approved on June 5, 2001. The study results are summarized below. Reference is made to the Summary of Safety and Effectiveness for a summary of this data (http://www.accessdata.fda.gov/cdrh_docs/pdf/P000008b.pdf).

The following information for the original indication is being provided to show the effectiveness and safety of the LAP-BAND[®] in a more obese patient population. In addition to difference in baseline weights for the patients in this study, excess weight was calculated using the midpoint of the 1983 Metropolitan Life Tables (equivalent to a BMI of about 22.5) instead of a BMI of 25. The different methods of calculating ideal weight results in a higher excess weight using the Metropolitan Life Tables compared to using a BMI of 25.

A. Design: Prospective, multicenter, non-randomized study trial in which each subject served as his or her own control. This study was approved in 1995.

B. Patient Selection Criteria:

Inclusion Criteria

1. Age 18-55
2. BMI \geq 40 OR 100 pounds above ideal weight
3. Willingness to comply with dietary restrictions
4. History of obesity for at least 5 years
5. Failure with non-surgical weight loss methods
6. Willingness to follow protocol requirements
7. Reside within a reasonable distance

Exclusion Criteria

1. High surgical risk
2. Personal or family history of inflammatory diseases of the gastrointestinal (GI) tract (including ulcers, esophagitis, irritable bowel syndrome)
3. Severe cardiopulmonary disease
4. Severe coagulopathy or upper GI bleeding conditions
5. Congenital or acquired anomalies of the GI tract such as atresias or stenoses
6. Severe hiatal hernia
7. Pregnant or intention of becoming pregnant in 12 months
8. Alcohol or drug addiction
9. Mentally retarded or emotionally unstable
10. Previous bariatric surgery, intestinal obstruction, or adhesive peritonitis
11. Infection

12. Family or personal history of systemic lupus erythemia, scleroderma, or other autoimmune connective tissue disorder
13. Participating in another study

C. Patient Demographics

A total of 299 patients were enrolled and 292 were implanted with the LAP-BAND® device at eight clinical sites in the United States. Seven patients who had previously been implanted with the Adjustable Silicone Gastric Band (ASGB), an earlier version of a gastric band, and had the ASGB band replaced with the LAP-BAND®, were not included in the study except for safety analyses of adverse events. Characteristics of the patients enrolled included:

<u>Characteristic</u>	<u>Mean Baseline Value (Range)</u>
Age (years)	38.8 (18-56)
Gender (female/male)	247 (84.6%)/ 45 (15.4%)
Weight (pounds)	293 (193-475)
Excess Weight (pounds)	156 (73-335)
Body Mass Index (kg/m ²)	47.4 (36.6-74.3)
Wt Gain in Prior 5 Years (pounds)	53.9 (-42 – 243)

Most patients had the device placed laparoscopically (259 versus 33 open). A total of 13 required actual conversion from laparoscopic to open placement. Average hospital length of stay for the laparoscopic procedures was 1.6 days (4.4 for open surgery).

D. Patient Follow-Up

Follow-up was performed at three weeks then at 3, 6, 9, 12, 18, 24, 30, and 36 months following implantation. Weight at each visit was used to calculate BMI, and compared to baseline weight and excess weight. Quality of life scores were assessed at 12 and 36 months using Beck Depression Index, and the RAND SF-36 scales.

E. Endpoints

Primary:

1. Percent excess weight loss (%EWL) at 1, 2, and 3 years
2. Incidence and severity of complications (device and non-device related)

Secondary:

1. Absolute weight loss
2. Change in excess weight
3. Change in BMI
4. Change in quality of life

F. Summary of Clinical Data at 3 Years

1. Effectiveness

Thirty-six (36) month effectiveness data was available in 178 patients (Table 1) and safety analyses in 183 patients (includes 4 ASGB patients and one patient with “invalid” weight data).

Table 1: %EWL by Visit

Visit	N	%EWL
6 months	233	26.5
12 months	233	34.5
24 months	189	37.8
36 months	178	36.2

As seen in Table 2, approximately 20% of subjects were able to lose at least 50% of their excess weight by three years.

Table 2: Percentage of Subjects with Subsets of %EWL

Excess weight loss at 3 years	% of Patients	# of Patients
Gained more than 5%EWL	2%	4
No change – 5% EWL	5%	9
Lost at least 25% EWL	62%	110
Lost at least 33% EWL	52%	93
Lost at least 50% EWL	22%	39
Lost at least 75% EWL	10%	18

Evaluation of the secondary endpoints also showed a mean absolute weight loss of 52.9 pounds (18% of body weight), mean excess weight loss of 53.4 pounds (34% of excess weight), and a decrease in BMI of 8.8 points.

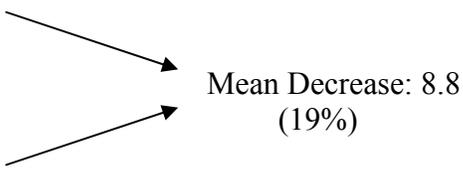
Secondary Endpoint:

<u>Time</u>	<u>Mean Weight (pounds)</u>	
Baseline	293.5	<p>Mean Loss: 52.9 (18%)</p>
6 months	254.5	
12 months	241.8	
24 months	234.5	
36 months	240.6	

Secondary Endpoint:

<u>Time</u>	<u>Mean Excess Weight (pounds)</u>	
Baseline	156.1	<p>Mean Loss: 53.4 (34%)</p>
6 months	117.0	
12 months	104.2	
24 months	97.4	
36 months	102.3	

Secondary Endpoint:

<u>Time</u>	<u>Mean BMI (kg/m²)</u>	
Baseline	47.5	
6 months	41.2	
12 months	39.0	
24 months	38.1	
36 months	38.7	

Quality of Life questionnaires showed improvement in all categories compared to baseline at both 12 and 36 months.

Results did not show any statistically significant differences among genders, race, age, diabetes, or method of operation.

2. Adverse Events

Eighty-nine (89) percent (266 patients) of the patients reported at least one adverse event (rated as “severe” in 34% of these patients) during the course of the study. The most common and important adverse events noted were:

<u>Adverse Event</u>	<u>% of Patients</u>
Nausea/Vomiting	51
GE Reflux	34
Abdominal Pain	27
Band Slippage	24
Stoma Obstruction	14
Constipation	9
Dysphagia	9
Diarrhea	9
Port Site Pain	9
Esophageal Dilatation	7
Incisional Infection	7
Band Erosion	1.3

Esophageal dilatation was an unexpected adverse event and was of concern to the FDA Advisory Panel that reviewed the submission in 2000. The incidence may be underestimated since it was not regarded as a potential adverse event at the start of the US study. Erosion of the device into the stomach, although a potentially serious complication, appears to be infrequent in occurrence. Both esophageal dilatation and band erosion were adverse events that were to be evaluated in the Post Approval Study.

A total of 26 patients required re-operation for band revisions or replacements (9%). Of these, 41% required placement of a new band. Approximately half were performed laparoscopically.

Seventy-five (25%) patients had explantation without immediate re-implantation. Forty-eight of these occurred during the study and 27 after the three year period. The most common reasons for explantation were band slippage and stoma obstruction (32%), GERD/dysphagia (11%),

esophageal dilation or dysmotility (7%), band erosion (5%), infection (4%), and system leak (4%). The sponsor notes that two-thirds of all explants occurred at three centers, suggesting investigator preference and experience. Forty of the explanted patients went on to have another type of bariatric surgery; gastric bypass in 37, and vertical-banded gastroplasty in three.

Two deaths occurred during the course of the study. One subject died from “mixed drug intoxication” one week after explantation. A second patient died one day after conversion to a Roux-en-Y, probably from multiple pulmonary emboli.

G. Conclusion

Effectiveness of the LAP-BAND[®] for the treatment of severe obesity with respect to long-term weight loss is less than that of other bariatric surgical procedures, but substantially better than traditional behavioral or medical therapy. Most of the weight loss that can be expected to occur happened within the first 12 months; however, it appears that the device is able to help a patient maintain a stable weight thereafter and, thus, may have a potential to significantly impact comorbidities that are frequently associated with obesity.

VII. Clinical Trial Design for Expanded Indication

A. Trial Name: Laparoscopic Adjustable Gastric Banding (LAP-BAND[®]) as a Treatment for Obesity in Subjects with BMI ≥ 30 kg/m² and < 40 kg/m²

B. Objective: To evaluate the safety and effectiveness of the LAP-BAND[®] System in an obese population (BMI ≥ 30 kg/m² and < 40 kg/m²)

C. Design: Prospective, multicenter, non-randomized study

D. Subjects and Investigational Sites: one hundred fifty-one (151) patients enrolled at seven (7) investigational sites in the United States

E. Randomization Scheme: there is no randomization scheme since the study was designed as a single arm, non-randomized study where subjects acted as their own controls. Subjects had already failed attempts at more conservative weight reduction methods. All subjects who met the eligibility criteria and passed the screening process were implanted with the device.

F. Endpoints:

Primary Effectiveness Endpoint: the study device was determined to be clinically effective if at least 40% of subjects achieved an excess weight loss (EWL) of 30% or greater at one year.

Percent EWL was defined as weight loss divided by excess weight multiplied by 100, where weight loss is equal to baseline weight minus follow-up weight, and excess weight is equal to baseline weight minus ideal weight.

$$\%EWL = \frac{\text{weight loss}}{\text{excess weight}} \times 100$$

where,

Weight loss = baseline weight – weight at follow-up

Excess weight = baseline weight – ideal weight

Ideal weight was determined based on a BMI of 25 kg/m². A subjects' ideal weight in pounds based on a BMI of 25 is equal to 25 divided by 703, multiplied by the subject's height in inches squared:

$$\text{Ideal Weight (lb)} = 25/703 \times [(\text{height (in)})^2]$$

Safety Endpoint:

The safety endpoint is the incidence and severity of adverse events (AE) related to treatment. Severity of an adverse event was rated by the investigator in accordance with the following scale:

- **Mild:** awareness of signs or symptoms, but easily tolerated.
- **Moderate:** discomfort sufficient to cause interference with normal activities
- **Severe:** incapacitating with inability to perform normal activities
- **Not applicable:** in some instances, an AE may be an 'all or nothing' finding which cannot be graded.

All adverse events were collected at each visit, including severity, relation to device, action taken, and outcome. Adverse events were followed by the investigational site throughout the study period until the event resolved.

Secondary Endpoints

All of the secondary endpoints were evaluated at 12 months and included:

1. Changes from baseline to month 12 in weight (evaluated as percent total weight loss [%WL])
2. Changes in health related quality of life as measured by the Impact of Weight on Quality of Life (IWQOL-Lite) assessment total score
3. Change in comorbid conditions of Type 2 diabetes, dyslipidemia and hypertension

Height and weight measurements were collected during the physical examination at each visit. Changes in comorbid conditions were also evaluated at each visit. Comorbid conditions were rated as mild, moderate, or severe per the following definitions:

- **Mild:** symptoms barely noticeable, or do not make subject uncomfortable, and/or prescription drugs are not needed.

- **Moderate:** symptoms make subject uncomfortable, performance of daily activities is influenced, and/or prescription drugs are needed to adequately control symptoms.
- **Severe:** symptoms cause subject severe discomfort, performance of daily activities is compromised, and/or condition is not entirely controlled with prescription drug therapy.

Subjects completed health related quality of life questionnaire prior to surgery and at 6 and 12 months post implant.

Additional Effectiveness Endpoints

Additional analyses included changes in various other weight variables (weight, excess weight, BMI, percent BMI loss), health related quality of life (SF36 health survey), depressive symptoms (Beck Depression Inventory II), eating behavior (Three Factor Eating Questionnaire and Questionnaire on Eating and Weight Patterns – Revised) and the economic impact of the implantation (Economic Impact Survey (EIS) were examined. Select measurements were analyzed at time points other than month 12, and longitudinal analyses for mean %EWL changes from baseline were conducted.

G. Statistical Hypothesis for Evaluation of Effectiveness Endpoints:

A formal hypothesis was established for the primary effectiveness endpoint, and the secondary endpoints of percent total weight loss and IWQOL-Lite assessment. P-values were provided for these effectiveness endpoints. The other secondary endpoint, status of comorbid conditions, was to be presented in terms of observed rates and confidence intervals only. Categorical variables were summarized using frequencies and percentages. Continuous variables and ordinal variables were summarized by the mean, median, standard deviation (SD), range of the values (minimum to maximum) and corresponding 95% confidence intervals (CI).

Before LAP-BAND[®] System placement surgery, investigators may have elected to place subjects on a very low calorie diet for about two weeks in order to reduce the size of the liver at surgery. For these subjects baseline corresponded to data collected at the screening visit in the calculation of weight related variables. For all other subjects, baseline corresponded to data collected at the surgery visit.

Primary effectiveness endpoint: the percent of subjects who attained clinically successful weight loss at one year post LAP-BAND[®] placement, where effectiveness was defined as having at least a 30% excess weight loss. At least 40% of the intent-to- treat subjects must have reached an excess weight loss of 30% or greater to achieve the primary endpoint. As defined in the protocol, the intent-to-treat dataset was to include only the actual (observed) data, without imputation. The primary effectiveness analysis was repeated for the per protocol population and for the complete implanted population treating subjects without data as failures.

Since the study did not include a control group (e.g., diet and exercise alone), the sponsor estimated that the background rate of subjects who would achieve a $\geq 30\%$ EWL in a one year period was 0-20%; that is, 0-20% of the population would obtain successful weight loss ($\geq 30\%$ EWL) at one year by diet and exercise alone. The endpoint “40% of subjects achieving $\geq 30\%$ EWL” was derived by defining a difference (Δ) of 20% as clinically meaningful; i.e., $\geq 40\%$ of subjects achieving EWL of 30% with the LAP-BAND[®] is clinically significant

compared with $\leq 20\%$ of subjects achieving EWL of at least 30% with diet and exercise alone. The primary effectiveness analysis was repeated for the per protocol population as a sensitivity analysis.

Secondary Effectiveness Analyses

All the secondary effectiveness analyses were conducted at 12 months. Two of the secondary endpoints (percent total weight loss and Impact of Weight on Quality of Life Total Score) were tested against a null hypothesis of no change from baseline (i.e., a null hypothesis mean of zero). For the change in comorbid conditions, only descriptive statistics were reported and 95% confidence intervals for the rate of improvement and resolution were provided.

- *Percent weight loss (%WL)* – changes in weight were analyzed as %WL and were defined as weight loss divided by baseline weight multiplied by 100, where weight loss is equal to baseline weight minus month 12 weight. The mean change from baseline was evaluated by a paired t-test.
- *IWQOL-Lite Total Scores* – the IWQOL-Lite consists of 31 items to assess weight related quality of life over five domains: *Physical, Self-Esteem, Sexual Life, Public Distress, and Work*. Scores ranged from 0 (worst) to 100 (best). The mean change in total IWQOL-Lite score from baseline to month 12 and its corresponding 95% confidence intervals were presented. The mean change from baseline was evaluated by a paired t-test or Wilcoxon signed-rank test, as appropriate. Effect size was calculated by Cohen’s statistical test, dividing the difference between the means at baseline and one year post implantation by the baseline standard deviation.
- *Comorbid conditions* – frequency of three comorbid conditions related to obesity (type 2 diabetes, dyslipidemia, and hypertension) was presented by severity (none, mild, moderate, and severe) at each time point. Post operative changes in severity (resolved, improved, unchanged, or worsened) from baseline were examined at month 12. Resolved was defined as moving into the “none” category, improved was defined as moving down at least one severity category, and worsened was defined as moving up at least one category. The percentage was calculated using the number of subjects with the existing comorbid condition at baseline as the denominator. Exact 95% binomial confidence limits were provided for the resolved and improved rate of the comorbid condition.

Other Effectiveness Analyses

- *%EWL* - Percent excess weight loss was summarized as a continuous variable at each of the follow-up time points. The mean change from baseline was evaluated by a paired t-test or Wilcoxon signed-rank test, as appropriate.
- *%weight loss, weight, excess weight (lb), BMI and % BMI loss* – were evaluated at all time points by a paired t-test or Wilcoxon signed-rank test, as appropriate.
- *Comorbid conditions* – 12 other comorbid conditions: back pain, depression, gallbladder disorder, gastroesophageal reflux, hypercholesterolemia, hypertriglyceridemia, metabolic

syndrome, osteoarthritis, respiratory abnormalities, sleep apnea, urinary incontinence, and venous stasis, were evaluated for changes at 12 months.

- *SF 36 Health Survey* – includes 36 questions that evaluate eight discrete domains. The score for each domain ranged from 0 (poorest health status) to 100 (best health status). The mean change from baseline was evaluated by a paired t-test or Wilcoxon signed rank-test, as appropriate. Effect size was calculated by Cohen’s d. The mean domain scores were also compared to general US population results by a two-sample t-test at baseline and month 12.
- *Beck Depression Inventory II* – consists of 21 questions to measure depressive symptoms and severity. Scores can range from 0 to 63 with higher total scores indicating more severe depressive symptoms. The subject’s worst response at the respective time point was used for any missing responses. The mean change from baseline was evaluated by a paired t-test or Wilcoxon signed-rank test, as appropriate.
- *Three Factor Eating Questionnaire* – designed to assess three dimensions of eating behavior: *Cognitive Restraint of Eating*, *Disinhibition* and *Hunger*. This is a two part questionnaire. The mean change from baseline was evaluated by a paired t-test or Wilcoxon signed-rank test, if appropriate.
- *Questionnaire on Eating and Weight Patterns-Revised* – a self-reported measure used to assess binge-eating disorder. Changes from baseline were tested using the McNemar test.

Safety Analyses

The incidence and severity of adverse events related to the treatment were tabulated and presented at each of the time points as well as overall for all intent to treat subjects. Exact 95% binomial confidence limits were provided; no statistical hypotheses were evaluated.

H. Analysis Populations:

All subjects who underwent surgery for placement of the LAP-BAND® were included in the analysis of safety and effectiveness. Two analysis populations were defined.

Intent-to-Treat (ITT) population: included all implanted subjects, was used in the main analysis for the primary and secondary effectiveness variables. Because the protocol specified that the primary analysis be performed without imputation, the sponsor also evaluated the “ITT evaluable” dataset which included only the observed data from each study visit. Imputation of missing values (e.g., last observation carried forward) was not performed for subjects who terminated prematurely or were lost to follow-up. As a sensitivity analysis the primary effectiveness endpoint was re-analyzed treating subjects with no data as failures.

Per Protocol (PP) population: included all subjects in the ITT population who were not considered to be influential protocol violators (defined as any deviation from the protocol that could affect the effectiveness analyses). If a subject in the PP population missed a

scheduled follow-up visit, the subject was excluded from the effectiveness analysis for that particular follow-up visit.

I. Follow up Schedule:

All enrolled patients were required to receive follow-up assessments to re-assess medical status and evaluate for the occurrence of adverse events. Assessments were made according to the schedule in Table 3. Patients will continue to be followed for five years after LAP-BAND® placement.

Table 3: Schedule of Follow-up Visits and Procedures

SC = Screening Visit BL = Baseline MO = Month WK = Week

Procedures	SC	-7 days	Surg. Day 0 BL	WK 1	Month																		
					1	2	4	6	8	10	12	15	18	21	24	30	36	42	48	54	60		
Informed Consent, HIPAA	X																						
Certification Page	X										X				X						X		
Inclusion/ Exclusion	X																						
Demographics	X																						
Medical History	X																						
PFT, Chest x-ray, EKG	X																						
Vital Signs (BP, HR, Temp, RR)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Comorbid Conditions	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical Exam	X										X				X		X	X	X	X	X		
Nutritional Evaluation	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Patient Food and Exercise Diary	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine Pregnancy Test (if female of childbearing potential)	X		X		X						X		X		X	X	X	X	X	X	X		
Gastrointestinal Evaluation	X																						
Esophagram	X										X				X		X		X		X		
Laboratory: Metabolic Hematologic Thyroid Panel Lipid Panel Liver Function Additional Pathology	X							X			X				X		X		X		X		
Urinalysis	X							X			X				X		X		X		X		

Procedures	SC	-7 days	Surg. Day 0 BL	WK 1	Month															
					1	2	4	6	8	10	12	15	18	21	24	30	36	42	48	54
Weight, BMI, Height, Waist, and Hip Measurements	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Psychosocial Evaluation	X																			
BDI-II		X					X			X		X		X	X	X	X	X	X	X
IWQOL-Lite, SF-36		X					X			X		X		X	X	X	X	X	X	X
TFEQ, QEWP-R		X					X			X		X		X	X	X	X	X	X	X
EIS		X								X				X		X		X		X
LAP-BAND® System Surgery			X																	
RNA Survey					X															
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fluoroscopy (if necessary)				(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
LAP-BAND® Adjustments (if necessary)					(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)

J. Patient Selection Criteria:

Selected Inclusion Criteria

- a. Had a BMI of $\geq 30 \text{ kg/m}^2$ and $<35 \text{ kg/m}^2$ with or without comorbid conditions or a BMI ≥ 35 and <40 without any severe comorbid conditions, where a comorbid condition is defined as severe if symptoms caused subject severe discomfort, performance of daily activities was compromised, and/or condition was not entirely controlled with prescription drug therapy
- b. Male or female, between 18 and 55 years of age
- c. History of obesity of at least two years including failed more conservative weight-reduction alternatives, such as supervised diet, exercise and behavior modification programs;
- d. Was physically and mentally able to comply with the visit schedule and behavior modification required for the LAP-BAND®, e.g., diet and exercise
- e. Was able to follow protocol requirements outlined in the protocol
- f. Had successful completion of the pre-screening, educational programs and psychological assessment supporting that the subject was an appropriate bariatric surgical candidate

Exclusion Criteria

- a. Family or subject history of congenital or acquired anomalies of the gastrointestinal tract, such as intestinal telangiectasia, intestinal malrotation, Grade 3-4 esophagitis, congenital abdominal wall defects, or inflammatory bowel disease (i.e., Crohn’s disease)
- b. Severe cardiopulmonary or other serious organic disease (thyroid disease, acute myocardial infarction, stroke, or cancer with the exception of non-melanoma skin cancer)

- c. Severe coagulopathies, hepatic insufficiency or cirrhosis
- d. History of intestinal obstruction or adhesive peritonitis
- e. History of bariatric, gastric or esophageal surgery
- f. History of esophageal dysmotility disorders
- g. Type I diabetes
- h. Pregnancy or intention of becoming pregnant during the study
- i. Uncontrolled psychiatric disorders (including untreated major depression, schizophrenia, substance abuse, bulimia nervosa), immaturity, or lack of family support which would potentially compromise the subject's ability to fully comprehend and/or cooperate with the study protocol
- j. Presence of localized or systemic infection at the time of surgery
- k. Chronic use of aspirin and/or non-steroidal anti-inflammatory medications and unwillingness to discontinue use
- l. Any conditions that are contraindicated in the LAP-BAND® System directions for use
- m. Significant weight gain or loss greater than 10% of body weight during screening (up until one week prior to surgery)
- n. Concurrent use of weight loss medications
- o. Current enrollment in an investigational drug or device study, or participation in such a study within 30 days of entry into the study
- p. A condition which in the investigator's opinion may put the subject at significant risk, may confound the results, or may interfere with the subject's participation in the study

VIII. Clinical Trial Results

A. Introduction

The pivotal trial for the LAP-BAND® Adjustable Gastric Banding System evaluated the use of the device in an obese patient population ($BMI \geq 30 - 40 \text{ kg/m}^2$). Current standard of care does not recommend bariatric surgery for this patient population, rather, these "lower BMI" patients are treated with diet and exercise or medication. The study was conducted to evaluate whether the use of the LAP-BAND® leads to more substantial and durable weight loss, and whether the risks associated with placement and long term use are acceptable.

B. Patient Accountability

A total of 151 patients were enrolled in the study (signed the informed consent) and 149 patients underwent LAP-BAND® placement. A total of 145 patients (97.3%) completed the 12-month followup. Four subjects discontinued their participation prior to 12 months. Patient accountability is summarized in Table 4.

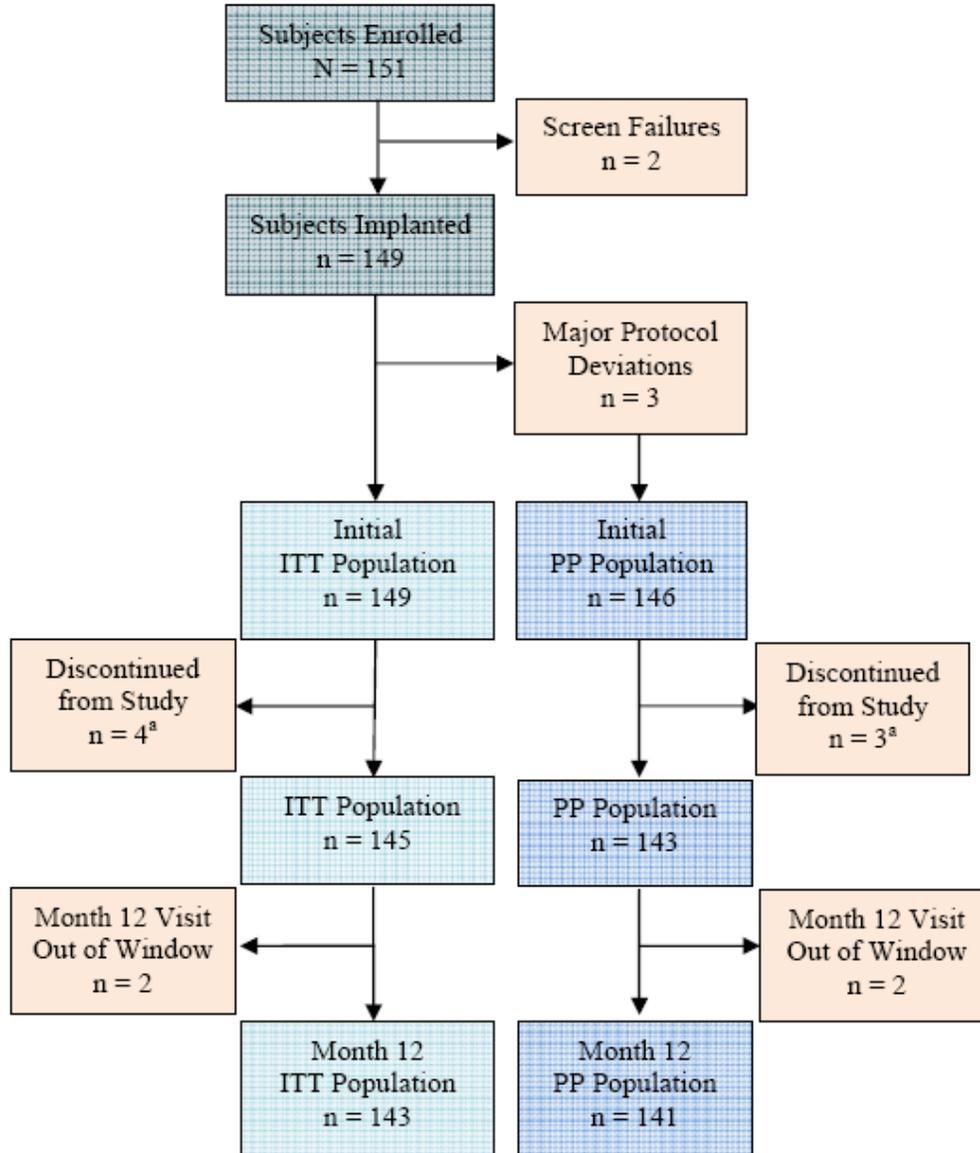
Table 4: Disposition of Subjects

Category	N	Percentage (%)
Total Enrolled	151	100.0%
Total Screen Failures	2	1.3%
Eligibility Criteria not met	2	100.0%
Consent withdrawn	0	0.0%
Other	0	0.0%
Total Implanted (ITT population)	149	98.7%
Completed Month 12 Visit	145 ^a	97.3%
Discontinued from Study	4	2.7%
Termination by Investigator/Allergan	0	0.0%
Lost to Follow-up	0	0.0%
Adverse Event	4	100.0%
Death	0	0.0%
Other	0	0.0%

^a includes two subjects whose 12 month visits fall outside visit window

Figure 3 shows the intent-to-treat and per protocol populations through month 12. In the information received on August 12, 2010, from the sponsor, they noted that although the study was approved for only 151 subjects, inspection of the study sites revealed an additional nine subjects who were enrolled (signed the Informed Consent), but failed further screening or chose not to participate and were not implanted. This resulted in subject numbers being re-used at three sites. The re-use of patient numbers accounts for some of the tables/charts showing an initial patient number of 160, and other tables showing an initial patient number of 151.

Figure 3: ITT and PP Populations through Month 12



^a three subjects were discontinued from both the ITT and PP, and an additional subject discontinued from the ITT population

C. Patient Demographic and Baseline Characteristics

Subjects were primarily female (n=135, 90.6%) and Caucasian (n=115, 77.2%) with a median age of 40 years and a mean baseline BMI of 35.4 (range 29.8 – 39.9). Mean weight at surgery was 214.9 pounds (range 152.6-286.2), with a mean excess weight of 62.8 pounds (range 28.8 - 100.7) (Table 5).

Table 5: Subject Demographics and Baseline Characteristics (N=149)

Characteristic (n=149)	N	%
Gender		
Female	135	90.6%
Male	14	9.4%
Age at Surgery Visit (Median, Range)		
	40.0 (18.0 – 55.0)	
18-20	5	3.4%
21-29	19	12.8%
30-39	46	30.9%
40-49	57	38.3%
50-55	22	14.8%
Race		
Caucasian	115	77.2%
Hispanic/Latino	16	10.7%
Black (not of Hispanic origin)	14	9.4%
Asian	2	1.3%
Other	2	1.3%
Age of Obesity Onset (Median, Range)		
	22.0 (5.0 – 51.0)	
≤ 20	69	46.3%
21-29	42	28.2%
30-39	28	18.8%
40-49	9	6.0%
50-55	1	0.7%
BMI (Mean, Range)		
	35.4 kg/m ² (29.8 kg/m ² - 39.9 kg/m ²)	
≥ 29 kg/m ² and < 30 kg/m ²	1 ^a	0.7%
≥ 30 kg/m ² and < 35 kg/m ²	63	42.3%
≥ 35 kg/m ² and < 40 kg/m ²	85	57.0%
Weight, pounds (Mean, Range)		
	214.9 (152.6 – 286.2)	
Ideal Weight, pounds (Mean, Range)		
	152.1 (121.7 – 216.3)	
Excess Weight, pounds (Mean, Range)		
	62.8 (28.8 – 100.7)	
Waist Circumference, inches (Mean, Range)		
	41.5 (33.5 – 53.5)	
Hip Circumference, inches (Mean, Range)		
	47.7 (37.0 – 55.9)	

^a Patient BMI was > 30 kg/m² at screening but < 30 kg/m² at surgery

D. Analysis of Treatment Administration

The surgical characteristics for the LAP-BAND® placement are presented in Table 6. Slightly more than half of subjects (55.7%) did not undergo a low calorie diet to reduce liver size prior to surgery. All of the surgeries were performed laparoscopically. Ninety eight percent (n=146) of the subjects were implanted with the AP Standard size of the LAP-BAND® while only 2% (n=3) of the subjects were implanted with the AP Large LAP-BAND®.

Table 6: LAP-BAND[®] Surgical and Device Characteristics

<i>Characteristic</i>	<i>n</i>	<i>%</i>
Low Calorie Diet Prior to Surgery		
No	83	55.7%
Yes	66	44.3%
Duration (days), Mean (Range)	9.8 (2-30)	
Surgical Method		
Laparoscopy	149	100.0%
LAP-BAND[®] Successfully Implanted		
Yes	149	100.0%
Device Style/Size		
AP Standard	146	98.0%
AP Large	3	2.0%
Time in Operating Room (minutes), Mean (Range)	41.0 (14.0-105.0)	

Over the first 12 months after device placement, subjects underwent a mean of 6.1 band adjustments (range of 0 to 14 adjustments). The first band adjustment was to take place 4-6 weeks after placement. Band adjustments occurred most frequently at month 1 (83.9% of subjects) and month 2 (92.6% of subjects). Total fill volume over the first 12 months was 4.77 ml (range 0-9.9ml).

E. Primary Effectiveness Results

1. Percent Excess Weight Loss at 12 Months

The primary endpoint was % excess weight loss (EWL). The study device was determined to be clinically effective if at least 40% of subjects achieved an excess weight loss of 30% or greater at one year. The sponsor achieved this with 80.5% of all implanted patients achieving this goal. In Table 7 the data are also provided as the excess weight loss for subcategories of weight loss (i.e., at least 25%, at least 30%, at least 50%). Sixty six percent (65.8%) of all implanted subjects lost at least 50% of their excess weight.

Table 7: Percent Excess Weight Loss at Month 12

	N	At Least 25% EWL ^a	At Least 30% EWL ^a	At Least 50% EWL
ITT – All Implanted ^b	149	127 (85.2%)	120 (80.5%) ^d	98 (65.8%)
ITT - Evaluable at Month 12 ^c	143	127 (88.8%)	120 (83.9%) ^d	98 (68.5%)
PP - Evaluable at Month 12	141	126 (89.4%)	119 (84.4%) ^d	97 (68.8%)

^a Cumulative frequency.

^b There were 6 subjects who did not have a Month 12 visit within the analysis window - 4 subjects discontinued (were explanted) prior to their Month 12 visit and 2 subjects had a Month 12 visit that was outside the analysis window. These subjects are treated as failures.

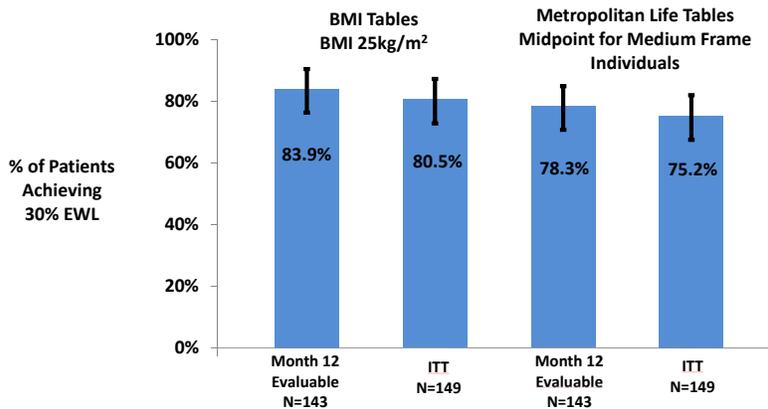
^c The pre-specified analysis method was without imputation, so this analysis only includes subjects who had a Month 12 visit within the analysis window (N=143).

^d P-value from exact binomial test against a null value of 40% is < 0.0001

The determination of excess weight for this study was based on an “ideal” weight of a BMI of 25. In the original PMA for the higher BMI subjects, the ideal weight was based on the midpoint of the Metropolitan Life (Met Life) Tables. Since the use of BMI of 25 as the ideal weight

results in a subject needing to lose less weight to achieve the same percentage of excess weight compared to the use of the midpoint of the Met Life tables, the sponsor was asked to provide a comparison table evaluating the success based on the use of both methods for determining ideal weight (Figure 4). For the ITT population the percentage of all implanted subjects that lost 30% excess weight using the Met Life tables was 75.2% compared to 80.5% when using a BMI of 25 for calculating ideal weight. The primary endpoint is met using either method for calculating ideal weight.

Figure 4: Comparison of Excess Weight Loss Using BMI Tables and Met Life Tables to Determine Ideal Weight



2. Weight and Body Mass Changes

All measures of weight and body mass at 12 months for the 143 evaluable subjects showed statistically significant improvements compared to baseline (Table 8).

Table 8: Summary of Weight and Body Mass Changes at 12 Months

Parameter	Baseline Mean (SD) n^a = 149	Month 12 Mean (SD) n = 143^b	Mean Change from Baseline at Month 12	95% CI^c (Lower, Upper)	P-value^d
Weight (lbs)	214.9 (24.3)	174.7 (24.5)	39.7	36.4, 43.0	<0.0001
%WL	N/A	18.3 (8.5)	18.3	16.9, 19.7	<0.0001
Excess Weight (lbs)	62.8 (16.1)	22.8 (19.4)	39.7	36.4, 43.0	<0.0001
%EWL	N/A	64.5 (30.3)	64.5	59.5, 69.5	<0.0001
BMI (kg/m ²)	35.4 (2.6)	28.8 (3.2)	6.5	6.0, 7.1	<0.0001
% BMI Loss	N/A	18.3 (8.5)	18.3	16.9, 19.7	<0.0001
Waist Circumference (inches)	41.5 (3.5)	35.4 (4.4)	5.9	5.4, 6.5	<0.0001
Hip Circumference (inches)	47.7 (3.0)	41.9 (3.5)	5.8	5.2, 6.4	<0.0001

N/A = Not applicable

^aBaseline is defined as the surgery visit for non-diet subjects and as screening for liquid diet subjects.

^bn is number of subjects with data available at Month 12 (no imputation was used)

^c95% CI is for the mean change from baseline

^dP-value is for the evaluation of mean change from baseline by means of a paired t-test

The typical patient lost 18.3% of baseline total weight, 64.5% of excess weight and BMI declined by 6.5 points. Other endpoints also steadily decreased over time.

Percent Weight Loss (%WL) – decreased 18.3% from baseline at month 12.

Change in Excess Weight – decreased from 62.8 lbs at baseline to 22.8 pounds at month 12.

Percent Excess Weight Loss (%EWL) – the mean excess weight decreased 64.5% from baseline to month 12.

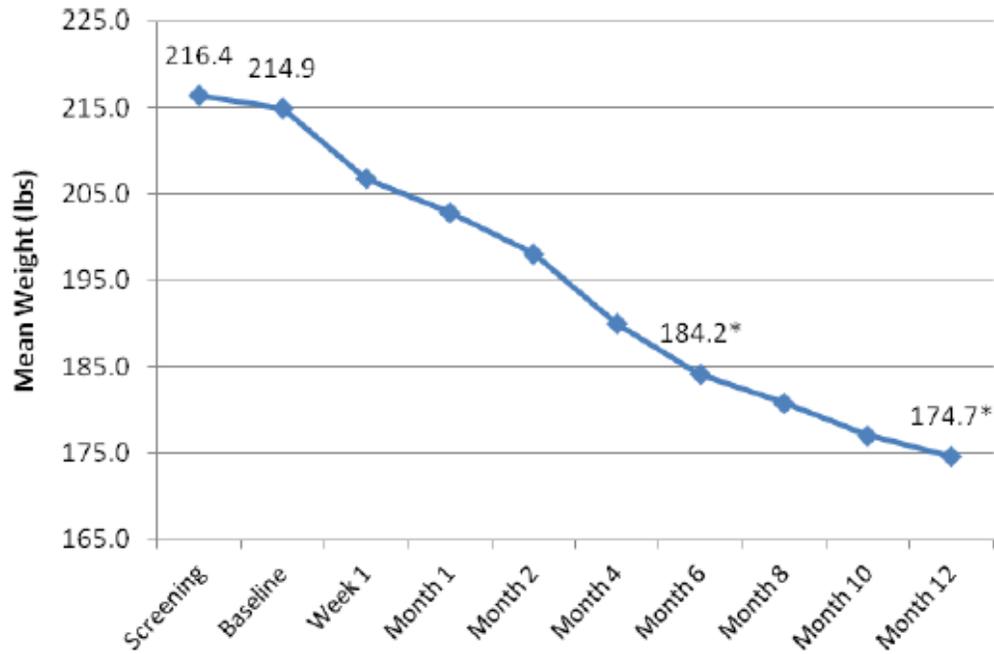
Waist circumference – decreased from 41.5 inches (range 33.5 – 53.5) at baseline to 35.4 inches (range 23.5 – 46.0) at month 12, with a mean change of 5.9 inches.

Hip Circumference – decreased from 47.7 inches (range 37.0 – 55.9) at baseline to 41.9 inches (range 35.0 – 50.5) at months 12 with a mean change of 5.8 inches.

Change in Weight (lbs)

The mean weight decreased from 214.9 lbs (range 152.6 – 286.2) at baseline to 174.7 lbs (range 128.8 – 262.5) at month 12. Figure 5 shows the steady decrease in mean weight through month 12.

Figure 5: Mean Weight through 12 Months



* $p < 0.0001$, calculated from the mean change from baseline. Mean weights are based on observed data (no imputation was used). Sample size for each point is based on number of subjects with weight data at that time point.

Change in BMI

For the 143 evaluable subjects (Table 9), the mean BMI decreased from 35.4 kg/m^2 at baseline to 28.8 kg/m^2 at month 12, with a mean decrease from baseline of 6.5 points ($p < 0.0001$). In Table 9, the data show that for all 149 implanted subjects, there was an overall shift in the distribution of subjects from the upper BMI range ($\geq 35 \text{ kg/m}^2$) to the lower BMI range ($< 30 \text{ kg/m}^2$). The number of subjects with BMI ≥ 25 and $< 30 \text{ kg/m}^2$ increased from 1 (0.7%) at baseline to 75 (50.3%) at Month 12, and the number of subjects with BMI $< 25 \text{ kg/m}^2$ increased from 0 at baseline to 19 (12.8%) at Month 12. The number of subjects with BMI between 30 and 35 kg/m^2 decreased from 63 (42.3%) at baseline to 49 (32.9%) after 12 months, and the number of subjects with BMI between 35 and 40 kg/m^2 decreased from 85 (57.0%) to 6 (4.0%) at Month 12. Overall, 148 subjects (99.3%) had BMI $\geq 30 \text{ kg/m}^2$ at baseline, and this number decreased to 55 subjects (36.9%) at 12 months. After one year with the LAP-BAND[®] System, 19 subjects (13.3%) were no longer overweight (BMI $< 25 \text{ kg/m}^2$) and an additional 75 subjects (52.4%) were no longer obese (BMI 25-30 kg/m^2). It should be noted that 36.9% of subjects would still be eligible for enrollment in the study because their BMI remained greater than 30 kg/m^2 .

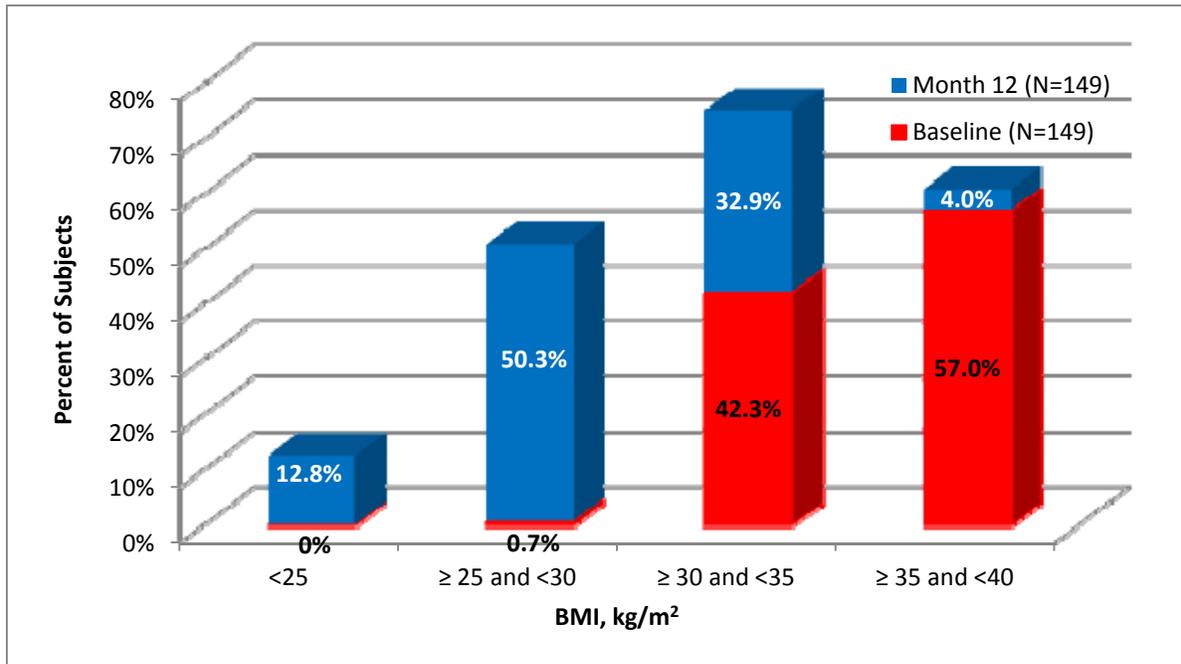
Table 9: Change in BMI Range from Baseline to Month 12 (N=149)

BMI Group	Baseline n (%)	Month 12 ^a n (%)
<25 kg/m ²	0	19 (12.8%)
≥ 25 and <30 kg/m ²	1 (0.7%)	75 (50.3%)
≥ 30 and <35 kg/m ²	63 (42.3%)	49 (32.9%)
≥ 35 and <40 kg/m ²	85 (57.0%)	6 (4.0%)
≥ 40 kg/m ²	0	0
Total	149 (100.0%)	149 (100.0%)

^aThere were 6 subjects who did not have a Month 12 visit within the analysis window - 4 subjects discontinued (were explanted) prior to their Month 12 visit and 2 subjects had a Month 12 visit that was outside the analysis window. For these subjects, their worst outcome/highest weight during the study is used for missing values.

Figure 6 shows the change in BMI by range of baseline BMIs at 12 months for all implanted subjects.

Figure 6: change in BMI Range from Baseline to 12 months (with imputation)



Other assessments were made, and all showed statistical significance. These included:

- Waist circumference
- Hip circumference
- Vital signs
- Co-morbid conditions

Comorbid Conditions

Table 10 summarizes comorbid conditions and their change in severity from baseline through the 12 month follow-up visit. The conditions in *italics* are evaluated as secondary endpoints while the other conditions are evaluated as additional endpoints.

Table 10: Comorbid Conditions Changes from Baseline to Month 12

Condition (n^a at surgery)	Resolved^b n (%)	Improved^c n (%)	No Change n (%)	Worsened^d n (%)
Back Pain (52)	18 (34.6%)	2 (3.8%)	31 (59.6%)	1 (1.9%)
Depression (41)	9 (22.0%)	1 (2.4%)	30 (73.2%)	0 (0.0%)
<i>Diabetes Type II</i> (6)	2 (33.3%)	0 (0.0%)	4 (66.7%)	0 (0.0%)
Dyslipidemia (29)	8 (27.6%)	0 (0.0%)	21 (72.4%)	0 (0.0%)
Gastroesophageal Reflux (42)	30 (71.4%)	0 (0.0%)	9 (21.4%)	0 (0.0%)
<i>Hypercholesterolemia</i> (38)	12 (31.6%)	0 (0.0%)	23 (60.5%)	1 (2.6%)
<i>Hypertension</i> (27)	6 (22.2%)	2 (7.4%)	19 (70.4%)	0 (0.0%)
Hypertriglyceridemia (9)	1 (11.1%)	0 (0.0%)	7 (77.8%)	0 (0.0%)
Metabolic Syndrome (1)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Osteoarthritis (57)	18 (31.6%)	0 (0.0%)	38 (66.7%)	1 (1.8%)
Respiratory Abnormality (38)	18 (47.4%)	1 (2.6%)	19 (50.0%)	0 (0.0%)
Sleep Apnea (11)	4 (36.4%)	1 (9.1%)	6 (54.5%)	0 (0.0%)
Urinary Incontinence (16)	8 (50.0%)	0 (0.0%)	8 (50.0%)	0 (0.0%)
Venous Stasis (11)	6 (54.5%)	0 (0.0%)	5 (45.5%)	0 (0.0%)

^a sum of the number of subjects in each category may not equal the total n at baseline due to missing data.

^b resolved was defined as subjects moving into the 'None' category

^c improved was defined as subjects moving down at least one severity category.

^d worsened was defined as subjects moving up at least one severity category.

There was a decrease in the number of subjects diagnosed with a comorbid condition after 12 months and certain comorbid conditions (i.e., GERD, metabolic syndrome, urinary incontinence, and venous stasis) were alleviated in more than 50% of the subjects who had the condition at baseline. The number of subjects with each comorbid condition is small; therefore, it is difficult to make definitive statements regarding improvement in the conditions.

Patient Reported Outcomes

Subjects completed two health related quality of life questionnaires (weight specific IWQOL-Lite, and SF-36), a measure of depressive symptoms (BDI-II), and two eating behavior measures (TFEQ and QESP-R) at baseline and at six and 12 months.

IWQOL-Lite – subjects reported a significant improvement (Table 11) for this measure at both six and 12 months compared to baseline. The improvement was statistically significant for all domains.

Table 11: IWQOL-Lite Changes from Baseline through Month 12

Visit	Score		Change in Score				
	n ^a	Mean (SD)	n ^a	Mean Change (SD)	95% CI (Lower, Upper)	P-value ^b	Effect Size ^c
IWQOL-Lite Total Score							
Baseline ^d	148	62.76 (18.295)	N/A				
Month 12	143	90.56 (12.364)	142	28.03 (17.274)	25.17, 30.90	<0.0001	1.52
IWQOL-Lite Physical Function							
Baseline ^d	148	61.02 (20.974)	N/A				
Month 12	143	92.76 (11.378)	142	31.83 (19.652)	28.57, 35.09	<0.0001	1.51
IWQOL-Lite Self Esteem							
Baseline ^d	148	44.38 (24.557)	N/A				
Month 12	142	80.56 (21.133)	141	36.80 (25.094)	32.63, 40.98	<0.0001	1.47
IWQOL-Lite Sexual Life							
Baseline ^d	144	66.36 (26.341)	N/A				
Month 12	143	89.29 (20.172)	139	22.66 (25.717)	18.35, 26.98	<0.0001	0.87
IWQOL-Lite Public Distress							
Baseline ^d	148	78.86 (19.931)	N/A				
Month 12	144	96.60 (10.253)	143	17.61 (17.757)	14.68, 20.55	<0.0001	0.89
IWQOL-Lite Work							
Baseline ^d	148	75.91 (21.310)	N/A				
Month 12	144	95.75 (10.125)	143	19.90 (20.649)	16.49, 23.31	<0.0001	0.93

^a n is the number of subjects; n's may differ due to missing data.

^b P-value is for the evaluation of mean change from baseline by paired t-test or Wilcoxon sign rank test based on p-value of normality test less than 0.05.

^c Cohen's d (based on each visit and baseline mean) indicates small (0.20 to 0.49), moderate (.50 to .79) or large effect ($\geq .80$).

^d Baseline is Surgery - 7.

It should also be noted that the same changes seen above were seen in the SF-36, Beck Depression Inventory-II, Three Factor Eating Questionnaire, and Questionnaire on Eating and Weight Patterns – Revised.

Subpopulation Analysis

Table 12 presents a summary of the primary effectiveness endpoint (percent of subjects with ≥ 30 %EWL) subpopulation analysis by gender, age, baseline BMI and ethnicity evaluated with and without the six subjects that were excluded from intent-to-treat population. Substantial weight loss was observed in all subpopulation groups, and more than 40% of subjects in every group achieved at least 30% EWL.

Table 12: Subpopulation Analyses of Primary Effectiveness Endpoint With and Without Imputation

Subpopulation	Without Imputation ^a		With Imputation ^a	
	n ^b	Subjects with at Least 30 %EWL at Month 12 ^c n (%)	n (+i) ^b	Subjects with at Least 30 %EWL at Month 12 ^c n (%)
Age, years				
18-29 (n=24)	22	19 (86.4%)	22 (+2)	19 (79.2%)
30-39 (n=46)	44	37 (84.1%)	44 (+2)	37 (80.4%)
40-49 (n=57)	55	44 (80.0%)	55 (+2)	44 (77.2%)
50-55 (n=22)	22	20 (90.9%)	22 (+0)	20 (90.9%)
Race				
Caucasian (n=115)	112	95 (84.8%)	112 (+3)	95 (82.6%)
Non-Caucasian (n=34)	31	25 (80.6%)	31 (+3)	25 (73.5%)
Gender				
Female (n=135)	132	111 (84.1%)	132 (+3)	111 (82.2%)
Male (n=14)	11	9 (81.8%)	11 (+3)	9 (64.3%)
BMI				
< 35 (n=64)	62	51 (82.3%)	62 (+2)	51 (79.7%)
≥ 35 (n=85)	81	69 (85.2%)	81 (+4)	69 (81.2%)
BMI and Baseline Comorbidity Status				
< 35 with comorbidities (n=56)	54	45 (83.3%)	54 (+2)	45 (80.4%)
< 35 without comorbidities (n=8)	8	6 (75.0%)	8 (+0)	6 (75.0%)
≥ 35 with comorbidities (n=71)	68	57 (83.8%)	68 (+3)	57 (80.3%)
≥ 35 without comorbidities (n=14)	13	12 (92.3%)	13 (+1)	12 (85.7%)
Investigational Site				
HL001 (n=14)	11	9 (81.8%)	11 (+3)	9 (64.3%)
HL002 (n=15)	15	13 (86.7%)	15 (+0)	13 (86.7%)
HL003 (n=30)	30	26 (86.7%)	30 (+0)	26 (86.7%)
HL004 (n=15)	13	10 (76.9%)	13 (+2)	10 (66.7%)
HL005 (n=15)	15	15 (100.0%)	15 (+0)	15 (100.0%)
HL006 (n=30)	30	25 (83.3%)	30 (+0)	25 (83.3%)
HL007 (n=30)	29	22 (75.9%)	29 (+1)	22 (73.3%)

^a Without imputation is the pre-specified primary endpoint analysis method. This analysis only uses observed data for the specified follow-up timepoint. The analysis with imputation is a sensitivity analysis, where imputed subjects are treated as failures.

^b n is the number of subjects with a visit within the analysis window and i is the number of imputed subjects at the specific follow-up visit.

^c Month 12 is based on the analysis visit window as defined in SAP.

Table 13 presents a summary of the BMI and % EWL subpopulation analysis by gender, age, baseline BMI and ethnicity. Substantial weight loss was observed in all subpopulation groups. In this table, the data reveal that although the sponsor is asking to remove the requirement for a comorbid condition for patients with a BMI between 35 and 40, in the clinical study only 14 of the 85 subjects with a baseline BMI of at least 35 had no comorbid condition.

Table 13: Subpopulation Analyses of BMI and % EWL

Subpopulation	Baseline ^a	Month 12 ^b			
	BMI Mean (SD)	N	BMI Mean (SD)	Change in BMI from Baseline Mean	%EWL Mean (SD)
Age, years					
18-29 (n=24)	35.90 (2.739)	22	28.65 (3.650)	7.21	66.27 (31.212)
30-39 (n=46)	35.79 (2.740)	44	28.73 (3.389)	6.97	66.28 (31.596)
40-49 (n=57)	35.15 (2.237)	55	29.14 (3.006)	6.04	61.17 (29.446)
50-55 (n=22)	34.41 (2.672)	22	28.25 (2.943)	6.16	67.61 (30.138)
Race					
Caucasian (n=115)	35.27 (2.580)	112	28.56 (3.216)	6.71	66.69 (30.420)
Non-Caucasian (n=34)	35.67 (2.556)	31	29.70 (3.042)	5.87	56.68 (28.961)
Gender					
Female (n=135)	35.43 (2.511)	132	28.86 (3.239)	6.51	64.31 (30.361)
Male (n=14)	34.74 (3.133)	11	28.17 (2.796)	6.71	66.98 (30.800)
BMI					
< 35 (n=64)	32.91 (1.566)	62	27.57 (2.764)	5.35	69.11 (34.289)
≥ 35 (n=85)	37.21 (1.330)	81	29.74 (3.213)	7.42	61.00 (26.524)
BMI and Baseline Comorbidity Status					
< 35 with comorbidities (n=56)	32.99 (1.539)	54	27.55 (2.735)	5.46	69.34 (33.025)
< 35 without comorbidities (n=8)	32.35 (1.748)	8	27.74 (3.145)	4.61	67.57 (44.550)
≥ 35 with comorbidities (n=71)	37.14 (1.267)	68	29.72 (3.157)	7.38	60.88 (26.338)
≥ 35 without comorbidities (n=14)	37.55 (1.621)	13	29.86 (3.627)	7.62	61.65 (28.576)
Investigational Site					
HL001 (n=14)	35.42 (2.543)	11	28.12 (2.213)	6.88	66.98 (25.384)
HL002 (n=15)	35.91 (2.597)	15	29.06 (3.289)	6.85	64.50 (28.418)
HL003 (n=30)	34.89 (2.716)	30	29.24 (2.876)	5.65	58.81 (26.409)
HL004 (n=15)	35.31 (2.145)	13	29.44 (3.161)	6.09	56.75 (30.329)
HL005 (n=15)	34.47 (2.969)	15	27.34 (3.614)	7.13	78.85 (34.065)
HL006 (n=30)	36.21 (2.096)	30	28.79 (2.997)	7.42	64.36 (29.420)
HL007 (n=30)	35.16 (2.783)	29	28.96 (3.798)	6.09	65.73 (35.356)

^a Baseline is defined as screening visit for subjects placed on the pre-surgery diet and surgery visit for subjects not on the pre-surgery diet.

^b Month 12 is based on the analysis visit window as defined in SAP. The pre-specified analysis method was without imputation, so this analysis includes the Month 12 Evaluable Population (N=143). There were 6 subjects who did not have a Month 12 visit within the analysis window - 4 subjects discontinued (were explanted) prior to their Month 12 visit and 2 subjects had a Month 12 visit that was outside the analysis window.

Laboratory Evaluations:

In general the findings demonstrate that for triglycerides, HDL, LDL, cholesterol, fasting glucose, and HbA1c, a majority of subjects with an abnormal value at the beginning of the study returned to normal range, with a small number of normals at initiation of the study becoming abnormal at 12 months.

FDA Comments on Effectiveness:

- Implantation with the LAP-BAND[®] Adjustable Gastric Banding System resulted in statistically significant decreases in all measures of weight loss. The primary effectiveness endpoint, greater than 40% of subjects achieving at least 30% excess weight loss at 12 months, was achieved ($p < 0.0001$); 83.9% of the ITT evaluable subjects ($n=143$) and 80.5% of the ITT subjects ($n=149$). The primary endpoint was met in 84.4% of the per protocol subjects. Over sixty five percent (65.8%) of subjects lost at least 50% of their excess weight. Other weight parameters were:
 - The mean percent weight loss (total weight loss) was 18.3% ($n=143$) at 12 months.
 - Excess weight decreased from a mean of 62.8 pounds at baseline to 22.8 pounds at 12 months ($n=143$).
 - The mean percent excess weight loss (%EWL) was 64.5% at 12 months ($n=143$).
 - Mean weight decreased 40.28 pounds at 12 months ($n=143$).
 - The mean BMI decreased 6.53 points at 12 months ($n=143$). Of the 149 implanted subjects, nineteen (19) subjects (12.8%) were no longer overweight ($BMI < 25 \text{ kg/m}^2$) and an additional 75 subjects (50.3%) were no longer obese ($BMI 25-30 \text{ kg/m}^2$).
 - Subpopulation analysis of the primary effectiveness endpoint and BMI by gender, age, baseline BMI and ethnicity showed substantial weight loss in all subpopulation groups, and more than 40% of subjects in every group achieved at least 30% EWL.
- The proportion of subjects who were obese ($\geq 30 \text{ kg/m}^2$) decreased from 99.3% at baseline to 36.9% at 12 months.
- Comorbid conditions showed a decrease in the number of subjects diagnosed with a comorbid condition after 12 months; however, there were relatively few numbers of subjects with each condition to allow in depth analysis.
- Health related quality of life was significantly improved after implantation with the LAP-BAND[®] System.

F. Primary Safety Evaluation

Adverse Events

During the 12 month period, 131 subjects (87.9%) experienced a total of 524 events. Table 14 shows the number of subjects that experienced at least one event, the number of events and the severity of the event.

Table 14: Summary of Adverse Event Frequency (N-149)

Condition ^a	Subjects n ^b (%)	Events n ^b (%)	Mild n ^b (%)	Moderate n ^b (%)	Severe n ^b (%)	N/A n ^b (%)
At least one event	131 (87.9%)	467 (100.0%)	244 (52.2%)	195 (41.8%)	27 (5.8%)	1 (0.2%)
At least one device related event	105 (70.5%)	215 (46.0%)	118 (54.9%)	92 (42.8%)	5 (2.3%)	0 (0.0%)
At least one non-device related event ^d	95 (63.8%)	251 (53.7%)	125 (49.8%)	103 (41.0%)	22 (8.8%)	1 (0.4%)
At least one unknown event	1 (0.7%)	1 (0.2%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total adverse Events ^e	131 (87.9%)	524				

^a AE dataset is summarized into three categories by relation to device. For subjects with multiple reports of the same adverse event, only the most severe event is counted.

^b n is the number of subjects having at least one AE in the corresponding AE category. Percentage is from the total population.

^c n is the number of events in the corresponding AE category. Percentage is from the total number of unique events.

^d includes events reported as Definitely or Possibly related.

^e includes all adverse events reported.

The sponsor counted 467 unique events (only the most severe occurrence of each event type; see “a” in footnote to Table 14, above). The majority of the events (251, 53.7%) were not related to the device, while 151 (32.3%) were definitely related to the device, and 64 (13.7%) were possibly related to the device.

A total of 105 subjects (70.5% of the total enrolled subjects) experienced a device-related adverse event (Table 15). The majority of device-related adverse events were mild in severity (n=118, 54.9%) and only 2.3% were severe (5 events in 3 subjects).

The most common device-related adverse events were vomiting (n = 43, 20.0%), dysphagia (n = 33, 15.3%), post-procedural pain (n = 28, 13.0%), and gastroesophageal reflux disease (n = 22, 10.2%). The remaining device-related adverse events occurred at a frequency of less than 4%.

Table 15: Device-Related Adverse Events ≥ 1%

Preferred Term	Events ^a		Mild	Moderate	Severe
	N	(%)	n (%)	n (%)	n (%)
Vomiting	43	(20.0%)	29 (67.4%)	13 (30.2%)	1 (2.3%)
Dysphagia	33	(15.3%)	20 (60.6%)	12 (36.4%)	1 (3.0%)
Post procedural pain	28	(13.0%)	1 (3.6%)	27 (96.4%)	0 (0.0%)
Gastroesophageal reflux disease	22	(10.2%)	15 (68.2%)	7 (31.8%)	0 (0.0%)
Abdominal pain	8	(3.7%)	2 (25.0%)	6 (75.0%)	0 (0.0%)
Nausea	8	(3.7%)	5 (62.5%)	3 (37.5%)	0 (0.0%)
Dyspepsia	7	(3.3%)	4 (57.1%)	3 (42.9%)	0 (0.0%)
Implant Site Pain	7	(3.3%)	6 (85.7%)	1 (14.3%)	0 (0.0%)
Abdominal pain upper	4	(1.9%)	3 (75.0%)	1 (25.0%)	0 (0.0%)
Constipation ^b	4	(1.9%)	3 (75.0%)	1 (25.0%)	0 (0.0%)
Medical device complication ^c	4	(1.9%)	2 (50.0%)	1 (25.0%)	1 (25.0%)
Dehydration	3	(1.4%)	1 (33.3%)	2 (66.7%)	0 (0.0%)
Device malfunction ^d	3	(1.4%)	0 (0.0%)	2 (66.7%)	1 (33.3%)
Shoulder pain	3	(1.4%)	1 (33.3%)	2 (66.7%)	0 (0.0%)

^a Events with frequency ≥ 1%

^b Investigators determined causality of AEs; constipation was variably attributed as device-related and non-device-related.

^c Complications included band erosion, tubing palpated in umbilical hernia, and band slippage

^d Malfunctions included partial slip, flipped port, and band slippage.

There was one occurrence of band erosion (treated with surgical explant), palpable tubing in an umbilical hernia (treated with abdominal wall hernia repair), and two occurrences of a “tight band” (treated by removing fluid from the band). Device malfunctions included two band slippage (treated with surgical revision, one of which was performed in year two), and a flipped port (surgical revision). There were two reports of esophageal dilatation (0.93%).

Of the 215 device related adverse events, no action was taken for 25 events (11.6%), medication was prescribed for 59 events (27.4%), and band adjustment (fluid removal) was performed for 108 events (50.2%). Surgical revision was performed for ten device related events in seven subjects and for one non-device related event (abdominal wall hernia repair).

No reoperations were necessary for the majority of subjects (95.3%). Seven subjects (4.6%) each required one reoperation, and there were no intraoperative complications. The mean time a subject spent in the operating room for a reoperation was 41.7 minutes (range, 15.0-81.0). Four of the seven reoperations (57.1%) were explants without replacement of band due to band erosion, abdominal pain, gastric carcinoid, and patient request due to dysphagia. Two of the seven reoperations (28.6%) were access port revisions due to a flipped port and port site pain. One reoperation (14.3%) was a revision to reposition the band with preservation of the same band due to band slippage.

There were no deaths or unanticipated adverse events. There were 17 events in 11 subjects that met the definition of a Serious Adverse Event (Table 16). The sponsor notes that only six (in four subjects) were related or possibly related to the device.

Table 16: Serious Adverse Events

Patient	Implantation Date	Onset Date	Adverse Event	Duration of Hospitalization	Resolution	Causality
█	2/23/2008	3/23/2008	Viral syndrome of unknown etiology	11 days	Medication	Not related
		11/29/2008	Band erosion	3 days	Explanted	Definitely related
		11/29/2008	Abdominal cavity abscess	7 days	Explanted	Definitely related
█	3/15/2008	4/16/2008	Abdominal pain	1 day	Explanted	Possibly Related
		4/19/2008	Bowel obstruction with ileus	7 days	Hospitalized	Not related
█	3/15/2008	6/3/2008	Gastric outlet obstruction	3 days	Fluid removal from band	Definitely related
		8/1/2008	Dysphagia	< 1 day	Explanted	Related
█	1/23/2008	7/21/2008	Biliary colic with biliary sludge	0	Outpatient cholecystectomy	Not related
█	1/15/2008	11/15/2008	Viral meningitis	3 days	Antibiotics	Not related
█	1/24/2008	12/2/2008	Cystocele	2 days	Hysterectomy	Not related
		12/2/2008	Worsening of uterine prolapse	2 days	Hysterectomy	Not related
█	5/6/2008	1/22/2009	Band slip	1 day	Band revision on 9/23/2009	Related
█	5/7/2008	3/9/2009	Kidney infection	3 days	Patient refused to release discharge summary	Not related
█	5/7/2008	5/28/2009	Endometrial hyperplasia	1 day	Hysterectomy, Salpingo-oophrectomy	Not related
█	1/29/2008	3/28/2008	Pulmonary embolism	5 days	Hospitalized	Not related
█	1/23/2008	10/12/2008	Bowel obstruction	3 days	Bowel resection and lysis of adhesions	Not related
		1/16/2009	Seizure	3 days	Hospitalized	Not related

FDA Comments on Safety

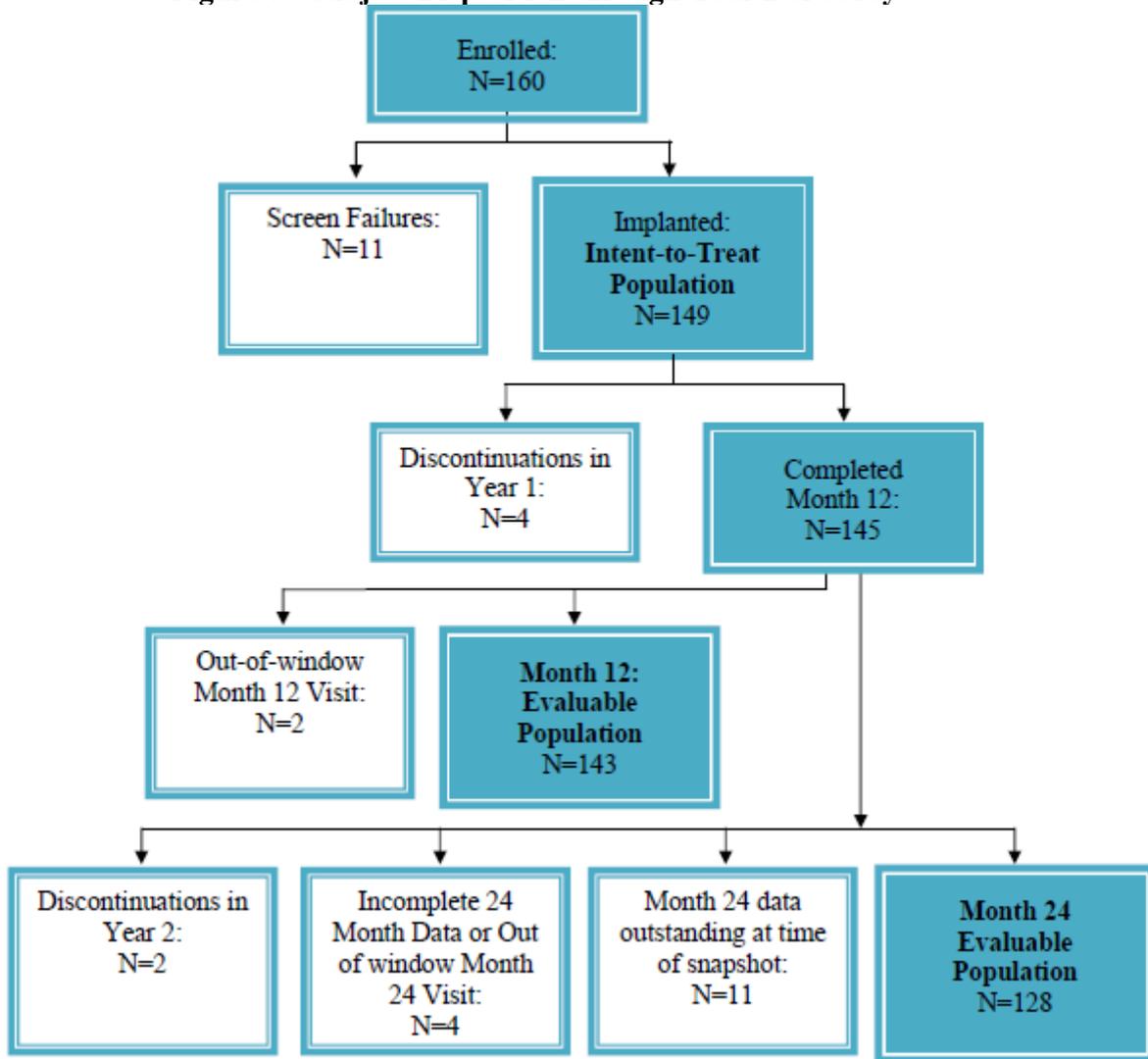
- There were no deaths or unanticipated adverse events.
- During the 12 month period, 131 subjects (87.9%) experienced a total of 524 events. The sponsor counted 467 of these events as the “most severe occurrence” of each event type. The majority of the events (251, 53.7%) were not related to the device, while 151 (32.3%) events were definitely related to the device, and 64 (13.7%) were possibly related to the device.
- A total of 105 subjects (70.5% of the total enrolled subjects) experienced a device-related adverse event. The majority of device-related adverse events were mild in severity (n=118, 54.9%) and only 2.3% were severe (5 events in 3 subjects).

- There were 17 events in eleven subjects that met the definition of a Serious Adverse Event; six of these events in four subjects were related or possibly related to the device.
- There was one occurrence of band erosion and two reports of esophageal dilatation in the first 12 months.
- Surgical revision was performed for ten device related events in seven subjects.
- Seven subjects each required one reoperation in the first 12 months; four of the seven reoperations were explants without replacement of band due to band erosion, patient request due to abdominal pain, gastric carcinoid, and dysphagia. Three of the explants occurred in males; 21.4% of males had the device removed. One of these three explants in male subjects followed obstruction associated with gastric carcinoid, and another was at the subject's request due to dysphagia (this subject had Crohn's disease, a contraindication for the LAP-BAND[®], of which the investigator was unaware at the time of implant). Two of the seven reoperations were access port revisions due to a flipped port and port site pain. One reoperation was a revision to reposition the band with preservation of the same band due to band slippage.

Two Year Update (update provided in Amendment 1)

Although the primary endpoint is 12 months post LAP-BAND[®] placement, the sponsor provided the available data on all evaluable subjects at two years in the "90 day update". The purpose of the submission was to inform the FDA of any significant new data, especially as it relates to safety. The sponsor also provided some effectiveness data on the available subjects. Figure 7 shows the number of subjects with two year data.

Figure 7: Subject Disposition through Year 2 of Study



Effectiveness Data

As previously reported, 83.9% of the 12 month evaluable population achieved at least 30% excess weight loss. At 24 months, 85.9% of the evaluable population, 128 subjects, were responders achieving at least 30% EWL (Table 17). In order to account for missing data, the sponsor also evaluated the data using Last Observation Carried Forward, Baseline Observation Carried Forward, and Worst Observation Carried Forward for the 138 subjects with 24 month data available. As presented in Table 16, all evaluations showed a significant responder rate.

Table 17: Month 24 Responder Rate (≥30% EWL)

Imputation Status	N	Number of Responders	Percent of Responders	95% Exact Binomial CI	P-Value^a
No Imputation	128	110	85.9%	78.69, 91.45	<0.0001
LOCF	138	118	85.5%	78.51, 90.92	<0.0001
BOCF	138	110	79.7%	72.03, 86.07	<0.0001
WOCF	138	110	79.7%	72.03, 86.07	<0.0001

^a P-value is from 2-sided exact binomial test to test the null hypothesis that 40% of subjects have at least 30% EWL. Note: LOCF - Last Observation Carried Forward, BOCF - Baseline Observation Carried Forward, WOCF - Worst (highest weight) Carried Forward

Table 18 provides the mean weight, at baseline and at 24 months, as well as percent weight loss (%WL) and percent excess weight loss (%EWL). Based upon this 24 month evaluation of the data, a mean of 20.1% weight loss (total weight loss) was achieved at 24 months, corresponding to a mean of 70.4% EWL for the 128 subjects.

Table 18: Summary of Weight and Body Mass Changes at 24 Months

Parameter	Baseline Mean (SD) n = 149	Month 24 Mean (SD) n = 128	P-value^a
Weight (lb)	214.9 (24.26)	171.0 (26.37)	<0.0001
%WL	N/A	20.1 (9.26)	<0.0001
%EWL	N/A	70.4 (32.29)	<0.0001

N/A = Not applicable

^a P-value is for the evaluation of mean change from baseline by paired t-test or Wilcoxon signed-rank test based on P-value of normality test <0.05.

The sponsor also evaluated percent excess weight loss and percent weight loss using a Last Observation Carried Forward, Baseline Observation Carried Forward, and Worst Observation Carried Forward to try and account for missing data. As presented in Table 19, the percent excess weight loss was 70.38% for the evaluable subjects and when evaluated using the “worst observation carried forward” the mean %EWL was still 65.18%. At 24 months the mean for percent weight loss was 20.11 for the evaluable subjects and 18.63% when using WOCF.

Table 19: Month 24 Mean %EWL and Mean %WL with and without Imputation

Variable	Imputation Status	N	Mean	SD	Median	Min, Max	95% CI
Percent EWL	No Imputation	128	70.38	32.289	72.3	3.8, 144.2	64.729, 76.024
	LOCF	138	69.07	32.177	70.2	3.8, 144.2	63.650, 74.483
	BOCF	138	65.28	36.080	66.6	0.0, 144.2	59.203, 71.350
	WOCF	138	65.18	36.279	66.6	-13.0, 144.2	59.070, 71.283
Percent WL	No Imputation	128	20.11	9.260	20.3	0.9, 40.4	18.493, 21.732
	LOCF	138	19.80	9.296	20.1	0.9, 40.4	18.239, 21.368
	BOCF	138	18.65	10.338	19.2	0.0, 40.4	16.915, 20.395
	WOCF	138	18.63	10.391	19.2	-3.4, 40.4	16.879, 20.377

The data for the effectiveness measures demonstrates that the device continues to be effective with maintenance and or progression of weight loss. In approximately 1/3 of the subjects there was a slight increase in BMI, in the majority of those subjects the increase was less than 1 kg/m² from year one to two. No subject returned to anywhere near their pre-op weight. A similar pattern was seen for the ITT analysis of weight gain.

Safety Data

The sponsor provided a reanalysis of the safety data from year one based on the clarification of some of the adverse events listed as serious adverse events, and then provided a table of these events from year one and again for year two. Investigators received clarification on how to report serious adverse events and their related symptoms during the second year of the study. This has resulted in some investigator reevaluation and corrections to serious adverse events reported in year one. There were 17 serious adverse events occurring in 11 subjects in year one and an additional 12 serious adverse events occurring in nine subjects in year two (Table 20).

Table 20: Summary of SAEs by year and cumulatively

	Year 1	Year 2	Total
Number of Subjects Experiencing at least 1 SAE	11	9	19
Number of SAEs	17	12	29

In year two a total of four reoperations were performed in four subjects (4/149 – 2.7% of subjects). Each of these four subjects underwent band reposition procedures following band slippage including in one subject who had reported the band slippage in year one of the study. Table 21 shows the reoperations for years one and two. There were no band removals in year two.

Table 21: Summary of Reoperations in Year 1 and Year 2

Reoperation Type	Year 1	Year 2
Intra-abdominal Reoperation		
Band removal without replacement	4	0
Band revision (same band)	1	4
Band revision with band replacement	0	0
Subcutaneous Reoperation		
Access port revision	2	0
Total	7	4

IX. Post-Approval Study Considerations

At the request of FDA, the sponsor submitted a protocol for the post-approval study to assess the long term effectiveness and safety post implantation of LAB-BAND[®] in the population as per new proposed indication.

The sponsor has proposed a prospective study to evaluate the effectiveness and safety at year five post-implantation. FDA reviews have fundamental concerns with the proposed study.

Objective:

The sponsor's stated objective for the proposed post-approval study is to evaluate the safety and effectiveness of the LAP-BAND[®] System in an obese population [body mass index (BMI) ≥ 30 kg/m² and < 40 kg/m²] after five years of implantation. Secondary objectives include assessment of changes in total weight, obesity-related comorbid conditions, and psychosocial functioning.

Enrollment and follow-up:

A total of 149 subjects with BMI ≥ 30 kg/m² and < 40 kg/m² were implanted with the LAP-BAND[®] System in the pivotal 5-year study (LBMI-001). The primary effectiveness for the PMA is evaluated at one year post surgery. The proposed PAS will be the full five-year study, with effectiveness to be assessed after 1 year post-implantation. Study data will be collected during regularly scheduled postoperative visits at months 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60.

Outcomes:

Effectiveness

The percent of subjects treated with the LAP-BAND[®] who achieve successful weight loss, at five years post-implantation, will be statistically greater than 40%, where successful weight loss is defined as at least 30% Excess Weight Loss (EWL).

Safety

Safety measurements will include the incidence of adverse events, by severity and relation to device, observed over the study assessment period.

Statistical Plan:

Sample Size Calculation

Sample size calculations were performed for the primary effectiveness endpoint of percent of subjects achieving at least 30% EWL. The sponsor stated that sample size was determined ensuring that the number of subjects available for the analysis at Year 5 would provide adequate statistical power and ample safety information. Based on the total ITT population of LBMI-001, the maximum number of subjects available at Year 5 is 149; at least 100 subjects are expected to be available for analysis. A sample size of 100 subjects will provide 82% power to detect differences as small as 15% from the null hypothesis that 40% of the subjects will obtain successful weight loss, using a two-sided, exact binomial test with $\alpha = 0.05$.

Effectiveness

All analyses will be performed on the ITT population, and, as a sensitivity analysis, the primary endpoint will also be analyzed for the PP population. The primary endpoint will be evaluated by a 2-tailed exact binomial test to determine if the proportion of LAP-BAND[®] subjects who achieve successful weight loss at 5 years post-implantation is statistically greater than 40%. Successful weight loss is defined as at least 30% EWL.

Safety

Safety analyses of the incidence of adverse events, by severity and relation to device, will be tabulated and presented with exact 95% confidence limits where appropriate. The ITT population will be used for all safety analyses.

FDA Comments on Proposed Post-Approval Study

1. Enrollment and follow-up

The sponsor proposed to follow patients enrolled in the IDE study up to five years post-implantation. The proposed study may lack generalizability and the study power may not be sufficient.

- a. The IDE study included sites with experience in clinical studies and investigational devices. The patient population is highly selected for the IDE study. The generalizability of these safety and effectiveness results to the broader patient population treated by other surgeons is of interest.
- b. The study power of the proposed PAS was evaluated for the primary effectiveness endpoint only. The study power was determined with the assumption that the primary success rate at year 5 will be at least 55%. The study power could be substantially lower when the success rate is only slightly lower. For example, if the success rate is 50%, the study power will be less than 50% with all the other assumption unchanged.
- c. The protocol did not evaluate the study power or accuracy for the safety endpoints.
- d. Although briefly mentioned in the section of statistically procedures, the protocol did not provide details for longitudinal analysis of the data. Results and changes of results throughout the study period will be very important information for the evaluation of safety and effectiveness of LAP-BAND[®], in addition to results at five years.

2. Outcomes and endpoints:

It is not clear how the endpoints were determined. The protocol did not describe the clinical basis for the criteria of effectiveness.

- a. It is not clear what the clinical basis is for the primary endpoint defined as at least 40% of patients with EWL% greater than or equal to 30%.
- b. It is not clear what the clinical basis is for the null hypothesis of 0 Percent WL at year five.
- c. The protocol does not provide details of safety evaluations. No specific endpoints were listed.

X. Conclusions

The data presented in the PMA supplement characterize the safety and effectiveness of the LAP-BAND[®] Adjustable Gastric Banding System for use in weight reduction for obese patients with a Body Mass Index of at least 35kg/m² or a BMI of at least 30 kg/m² with one or more comorbid conditions.

The sponsor has drawn the following conclusions from their analysis of the data:

- The data demonstrate implantation with the LAP-BAND[®] Adjustable Gastric Banding System resulted in statistically significant decreases in all measures of weight loss at 12 months.
- Comorbid conditions showed a decrease in the number of subjects assessed as having a comorbid condition after 12 months.
- Health related quality of life was significantly improved after implantation with the LAP-BAND[®] System.
- Safety findings were similar to or better than those in previously reported subjects with a BMI greater than 40 kg/m² who received the LAP-BAND System. There was a low occurrence of serious adverse events.

FDA reviewers have also analyzed the data extensively and believe that the study met the primary endpoint and that there was significant decrease in all measures of weight loss. There are, however, several questions regarding the study that FDA will be asking the Panel to comment on.

- FDA will be asking the panel to address the issue of how closely the enrolled population represents the US population that would be eligible to receive the device and whether there are any concerns regarding that in the clinical study, the majority of subjects were Caucasian females and that men non-Caucasians were underrepresented.
- FDA will be asking the panel a question regarding the amount of weight loss that would be considered clinically meaningful in the lowest BMI patient population.
- FDA will be asking the panel a question on whether the results of the study are adequate to change the current practice of medicine to recommend LAP-BAND[®] surgery in these patient populations.