P130019
MAESTRO RECHARGEABLE SYSTEM FOR TREATMENT OF OBESITY

BRIEFING DOCUMENT FOR THE GASTROENTEROLOGY AND UROLOGY DEVICES PANEL

MEETING DATE: June 17, 2014

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
BDI-II	Beck Depression Inventory-II
BMI	Body Mass Index
CEC	Clinical Events Committee
DSMB	Data and Safety Monitoring Board
DPP	Diabetes Prevention Program
EWL	Excess Weight Loss
FDA	Food and Drug Administration
GUDP	Gastroenterology and Urology Devices Panel
GI	Gastrointestinal
HDL	High-Density Lipoprotein
IDE	Investigational Device Exemption
ITT	Intention-to-Treat
IWQoL-Lite	Impact of Weight on Quality of Life-Lite
LAGB	Laparoscopic Adjustable Gastric Banding
LDL	Low-Density Lipoprotein
LOCF	Last Observation Carried Forward
MTV	Maximum Tolerated Volume
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
PMA	Pre-Market Approval
PP	Pancreatic Polypeptide
RYGB	Roux-en-Y Gastric Bypass
SAE	Serious Adverse Event
TBL	Total Body Weight Loss
TFEQ	Three Factor Eating Questionnaire
UADE	Unanticipated Adverse Device Effect

1 SYNOPSIS

The Maestro Rechargeable System provides a new option for patients who are seeking clinically significant weight loss. As described in this document, the Maestro Rechargeable System is a safe and effective treatment option for obese individuals who have failed more conservative weight reduction interventions such as diet/exercise and pharmacotherapy, but are not able or willing to undergo more aggressive bariatric surgical options.

Obesity in the United States has reached epidemic levels. Two of every three adults in the U.S. are either obese or overweight. One of the most significant challenges facing clinicians in treating obese patients is the limited number of safe, effective, and acceptable treatment options.

The Maestro Rechargeable System delivers intermittent electrical blocking signals to the anterior and posterior trunks of the intra-abdominal vagus nerve (termed VBLOC® Therapy). The therapeutic mechanism behind the device is blocking vagus nerve signals reduces sensations of hunger and produces satiety leading to weight loss. The system consists of a rechargeable neuroregulator with flexible leads, mobile charger, transmit coil, AC recharger, and clinician programmer. The neuroregulator is implanted under the skin on the lateral chest wall. The flexible leads are laparoscopically placed around the vagal trunks at the gastroesophageal junction.

The ReCharge Study is the pivotal study supporting approval of the Maestro System. ReCharge is a randomized, double-blind, sham-controlled clinical trial. It is the first study of its kind for obesity treatment that has been brought to the Gastroenterology and Urology Devices Advisory Panel. In order to maintain the blind of patients and follow-up personnel to randomization assignment, the study's control arm received both a sham surgical procedure and a sham neuroregulator. The sham surgery mimicked implantation with the active device and included general anesthesia with abdominal skin incisions to simulate laparoscopic lead implantation. The implanted sham device required daily interaction and recharging similar to the active device.

The primary safety endpoint of the ReCharge Study was the rate of device, procedure, or therapy-related serious adverse events (SAEs) in the group receiving active VBLOC therapy at 12 months. The objective was to demonstrate a primary safety SAE rate less than the 15% performance goal.

The study had two co-primary efficacy objectives defined in terms of percentage excess weight loss (%EWL) from implant. The objective was to demonstrate super-superiority, which required that the lower bound of the 95% confidence interval for the treatment difference had to exceed 10 percentage points. This differs from a conventional test for superiority where the lower bound only has to be greater than zero. The study was powered assuming a mean 25% EWL in the VBLOC group and 5% EWL in the sham control group at 12 months. The second efficacy objective was to demonstrate that at least 55% of VBLOC subjects achieved at least 20% EWL and 45% of subjects achieved at least 25% EWL.

ReCharge randomized 162 patients to receive a Maestro Rechargeable System with VBLOC therapy and 77 subjects to receive implantation with a sham device. Of these 239 patients, 233 (157 VBLOC, 76 sham control) were ultimately implanted. Data from all randomized patients were used in the intention-to-treat analysis of the study endpoints using the last observation carried forward imputation method (ITT-LOCF), which included subjects who were not implanted.

ReCharge met its primary safety endpoint with a primary SAE rate of 3.7% (95% CI: 1.3% to 7.9%, $p<0.0001$) at 12 months. Non-serious treatment-related adverse events were predominantly transient side effects of VBLOC therapy, which were typically reported as mild to moderate heartburn, dyspepsia, and discomfort.

In the ITT-LOCF population at 12 months, the VBLOC group achieved a mean 24.4% EWL compared to 15.9% EWL in the sham control group with a treatment difference of 8.5 percentage points (95% CI: 3.1 to 13.9). The study demonstrated superiority of VBLOC over sham control, however the super-superiority objective was not met. While the VBLOC group achieved the mean %EWL assumed in the study design, the sham control weight loss was three times greater than anticipated in the study design. The majority of subjects in the VBLOC group (52.5%) achieved a clinically significant 20% EWL and 38.3% achieved at least 25% EWL, which slightly missed the performance targets.

In a responder analysis comparing VBLOC to sham patients, the odds of achieving clinically meaningful weight loss thresholds increased considerably for VBLOC with higher, more difficult to attain, responder levels. While the study did not pre-specify endpoints for patient questionnaires or cardiovascular and metabolic risk factors, these measures were assessed for clinical relevance as post-hoc analyses. Patients reported significant improvements from baseline in quality of life and eating behaviors. The only measure that was significantly different between groups was the reported feelings of hunger, which is consistent with VBLOC's mechanism of action. Improvements in cardiovascular and metabolic risk factors were commensurate with weight loss.

Longer-term follow-up demonstrated that the weight loss achieved by VBLOC was maintained through 18 months. Interestingly, the sham control group regained over 40% of the weight lost in the first 12 months and the majority of this regain preceded patients being unblinded to their randomization to the sham control arm.

In summary, the ReCharge Study demonstrates that VBLOC therapy provides a safe and effective treatment option with a positive benefit-risk profile for obese individuals. It provides a needed therapeutic treatment option that currently does not exist for patients who have failed more conservative weight reduction alternatives.

2 EXECUTIVE SUMMARY

2.1 UNMET MEDICAL NEED IN TREATMENT OF OBESITY

Obesity in the United States has reached epidemic levels. Two of every three (68.8%) adults in the U.S. are either obese (body mass index (BMI) ≥30 kg/m^2) or overweight (BMI 25-29.9 kg/m^2), and one in fifteen adults is categorized as extremely obese (BMI ≥40 kg/m^2).[1]

In the U.S., published estimates of deaths related to obesity have ranged from 112,000 to 400,000 per year, making obesity one of the leading causes of preventable death.[2] A large mortality study found that median survival is reduced by 2-4 years in obese individuals (BMI 30-35 kg/m^2) and is reduced by 8-10 years among extremely obese individuals (BMI 40-45 kg/m^2) compared to individuals with optimal BMI (22.5-25 kg/m^2); an increase of 5 kg/m^2 in BMI from the optimal BMI was associated with nearly 30% higher risk for mortality.

Obesity is linked to serious health problems such as cancer, diabetes, and heart disease. For example, the National Health and Nutrition Examination Survey (NHANES) 1999-2004 data showed that obese individuals have a higher prevalence of conditions such as Type 2 diabetes, hypertension, and dyslipidemia compared to normal weight individuals.[19] Weight loss can improve or resolve comorbid conditions.[3] In the U.S. Diabetes Prevention Program (DPP) study, total body weight loss (TBL) of 7.0% reduced the risk of diabetes by 58% and delayed diabetes onset by about two years.[4] Weight loss also improved metabolic syndrome and cardiovascular risk factors such as hypertension and hyperlipidemia with an overall reduction in the use of pharmacologic therapy.[5,6] The Finnish National Diabetes Prevention Program demonstrated a reduction in the relative risk of diabetes as well as reduction in other cardiovascular risk factors in patients who lost more than 2.5% TBL, with a worsening of risk factors among those who gained weight.[7] The Nurses' Health Study showed that weight loss in overweight women was associated with improved physical function and vitality, and decreases in bodily pain.[8]

Unfortunately for many people with obesity, diet and exercise alone do not provide sustainable, clinically meaningful weight loss. Studies have shown that a low percentage of patients who use conservative treatments (e.g., behavioral therapy, diet and exercise) achieve meaningful, sustained weight loss.[9,10,11] Currently, orlistat, phentermine-topiramate and lorcaserin are the only FDA-approved obesity drugs commercially available and approved for long-term treatment. Although these drugs have been shown to be effective, published studies demonstrate that 30-50% of patients drop out of the studies during the first year, often due to side effects or dissatisfaction with the level of weight loss.[12,13,14 15,16]

Bariatric surgical procedures, such as Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), and sleeve gastrectomy are effective in achieving substantial weight loss. On average, RYGB results in weight loss of 55-60% excess weight loss (EWL), but it is also associated with substantial short- and long-term morbidity, including anastomotic leak, intra-abdominal abscess, stricture, bowel obstruction and nutritional deficiencies.[17,18,19,20]

LAGB is another effective surgical weight loss option, with typical weight loss of 35-45% EWL on average among patients who complete the studies.[21] Postoperative complications of LAGB include band slippage/pouch dilatation and band erosion. Recent consensus practice guidelines cite the overall post-operative complications of LAGB as 1-3% with longer term complication rates of 3-4% for band migration or misplacement, 1% for erosion of the gastric wall and 5-11% for port complications. The failure rate, leading to removal of the band, is up to 34%.[22]

Therefore, while conventional bariatric operations often result in substantial weight loss, the complex morbidity profiles of the procedures appears to be a reason of concern for many patients. Additionally, many potential surgical candidates consider the necessary post-operative dietary restrictions to be unacceptable. As a result of these factors, it has been estimated that less than 1% of US patients who are eligible in a given year ultimately undergo a bariatric procedure.[23]

A review of the treatment options for obesity illustrates the large, unmet clinical need for new obesity therapies. Many patients with morbid obesity have failed to sustain weight loss after multiple attempts with diet, exercise, and medications. Currently, the only remaining clinical option for these patients is a conventional anatomy-altering bariatric procedure, which has proven to carry unacceptable risks for many eligible patients. VBLOC therapy with the Maestro Rechargeable System was designed to bridge the gap of benefits and risks between diet, exercise, and drug therapy and conventional bariatric surgery.

As described in this document, the ReCharge Study demonstrates that VBLOC therapy provides a safe and effective treatment option for obese individuals and fills a therapeutic void that currently exists for patients who have failed diet/exercise and/or pharmacotherapy, but who are either not able or are unwilling to undergo more aggressive surgical options that permanently alter gastrointestinal anatomy.

2.2 OVERVIEW OF MAESTRO RECHARGEABLE SYSTEM

The Maestro Rechargeable System delivers electrical blocking signals to the anterior and posterior trunks of the intra-abdominal vagus nerve. The therapeutic mechanism behind the device is blocking vagus nerve signals reduces the sensation of hunger and produces satiety, leading to weight loss.

The system consists of a rechargeable neuroregulator with flexible leads, mobile charger, transmit coil, AC recharger, and clinician programmer and programmer cable. The neuroregulator is subcutaneously implanted into the lateral chest wall. The flexible leads are laparoscopically placed around the vagus nerve.

The mobile charger and transmit coil are used to check the charge level in the neuroregulator battery and recharge the battery when necessary. The AC recharger is used to charge the internal battery of the mobile charger and is adaptable to 120 or 220 volt electrical source.

The clinical programmer is a commercially available laptop computer with a proprietary software program that communicates with the mobile charger and neuroregulator. Clinicians

use the programmer to modify therapy parameters and therapy schedules as well as to retrieve diagnostic information.

2.3 INDICATION FOR USE

EnteroMedics submitted an application to the FDA requesting Premarket Approval for the Maestro Rechargeable System with the following proposed indication:

> *The Maestro Rechargeable System is indicated for use in weight reduction in adult patients with obesity who have a Body Mass Index (BMI) of at least 40 kg/m^2, or a BMI of at least 35 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.*

2.4 PRE-CLINICAL ANIMAL AND CLINICAL MECHANISM OF ACTION STUDIES

Pre-clinical studies evaluated vagal nerve blocking therapy for safety and to determine the appropriate algorithm to initially evaluate in humans. The studies are described in more detail in Section 3.6 of this document. The studies show that application of 5000 Hz (VBLOC therapy) inhibits compound action potential propagation in the rodent model and down regulates pancreatic exocrine secretions and gastric contractions in the juvenile porcine model. Preclinical studies demonstrate that vagal nerve blocking is reversible and safe.

Clinical mechanism of action studies were performed in humans to assess calorie intake and dietary composition, inhibition of plasma pancreatic polypeptide and maximum tolerated volume. These studies show that, compared to baseline, chronic delivery of VBLOC therapy results in a reduction in food intake, inhibition of plasma pancreatic polypeptide (PP), and a reduction in maximum tolerated volume (MTV) ingested. These studies are also described in more detail in Section 3.7 of this document.

2.5 PRIOR CLINICAL STUDIES

Two early clinical studies, EMPOWER and VBLOC-DM2, were conducted to support the safety and effectiveness of VBLOC therapy. These studies are described in more detail in Sections 3.8 and 3.9 of this document.

2.6 RECHARGE STUDY

The ReCharge Study is the pivotal study to establish the safety and effectiveness of the Maestro Rechargeable System.

2.6.1 Study Design

ReCharge is a randomized, double-blind, sham-controlled trial of 239 subjects at 10 investigational sites in the United States and Australia. Subjects were enrolled with a BMI 40 kg/m^2 to 45 kg/m^2 or BMI 35 kg/m^2 to 39.9 kg/m^2 with at least one obesity related co-morbid condition. Subjects with type 2 diabetes were limited to 10% of the total sample, with no more than three diabetic subjects enrolled per center. Subjects were randomized 2:1 to be implanted with either VBLOC delivered by the Maestro Rechargeable System or the sham control device.

Subjects randomized to the sham control group received both a sham surgical procedure and a sham implanted device. The sham surgical procedure mirrored the procedure received by the VBLOC subjects, including general anesthesia and incisions simulating the laparoscopic placement of the leads but no leads were implanted on the vagal trunks. They were implanted with a modified, functional neuroregulator that dissipated charge into resistors. In addition, sham control subjects had to interact with their device on a daily schedule, including checking the battery level and recharging their neuroregulator, in a manner similar to VBLOC subjects.

All subjects participated in a standard weight management program throughout the study, which consisted primarily of 15-minute counseling sessions. The weight management program did not incorporate intensive interventions, such as a very low calorie diet, portion-controlled meals, mandatory exercise program, behavioral modification, or weight loss pharmacotherapy. Table 2-1 displays the interventions received for each group in the ReCharge Study.

Table 2-1: Interventions in ReCharge Study

Study Intervention	VBLOC	Sham Control
General anesthesia and small skin incisions	X	X
Implanted neuroregulator	X	X
Laparoscopically-implanted leads (VBLOC therapy)	X	
Daily device check with charger	X	X
Battery depletion and recharging	X	X
Follow-up visits with weight management counseling	X	X

Following the blinded 12-month portion of the trial, sham control patients were given the opportunity to cross over to an active Maestro Rechargeable System. Follow-up will continue for all patients for 5 years post-implant.

2.6.1.1 Study Endpoints

There were two co-primary efficacy endpoints. The first co-primary efficacy endpoint was to demonstrate super-superiority in %EWL with a mean treatment difference statistically greater than 10 percentage points between the VBLOC and sham control groups at 12 months post-randomization. Unless otherwise specified, %EWL will be computed using the BMI method in this document.

The %EWL using the BMI method is calculated as:

*%EWL = (weight lost) / (baseline weight – ideal body weight) * 100%*

Ideal body weight is the weight corresponding to a BMI of 25 given the subject's height.

The second co-primary efficacy endpoint was to demonstrate:

- At least 55% of VBLOC patients achieve at least 20% EWL, and
- At least 45% of VBLOC patients achieve at least 25% EWL

The primary safety objective was to demonstrate that the 12-month implant/revision procedure, device, or therapy-related SAE rate was significantly lower than 15% in the VBLOC group. The 15% performance goal was based on the SAE data available on the approved labels for LAGBs.

2.6.1.2 Statistical Methodology

All primary analyses were conducted under the ITT principle and included all randomized subjects. Subjects without a 12-month weight had their weight imputed using the last observation carried forward (LOCF) method for the primary ITT analysis per the statistical analysis plan. There were six (5 VBLOC, 1 sham) subjects who were not implanted and had 0% EWL imputed for the primary effectiveness endpoints.

2.6.2 Subject Disposition and Baseline Characteristics

From May 16 to December 27, 2011, 162 subjects were randomized to the VBLOC group and 77 to the sham control group. At 12 months, 93.7% of subjects remained in the study. One hundred and forty-seven (90.7%) subjects in the VBLOC group and 66 (85.7%) subjects in the sham control group completed their 12-month follow-up visit. At 18 months, 86% of subjects were still enrolled in the study.

At baseline, the average age was 47 ± 10 years, 85% of subjects were female, the average BMI at implant was 40.9 ± 2.9 kg/m^2, and thirteen subjects (5.4%) had diabetes mellitus. The groups were well balanced on demographic and medical history variables of interest. Detailed information on baseline information is shown in Table 4-5.

2.6.3 Efficacy Results

2.6.3.1 First Co-Primary Efficacy Endpoint

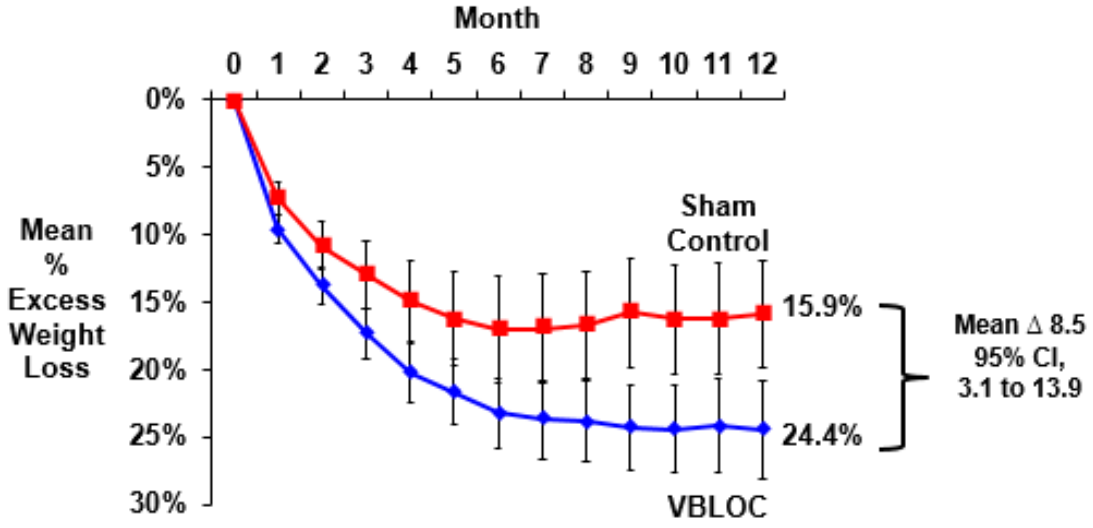
The mean %EWL in the VBLOC group was 24.4% at 12 months compared to 15.9% in the sham control group (Table 2-2). The mean difference between groups was 8.5 percentage points (95% CI, 3.1 to 13.9), demonstrated superiority of VBLOC over sham control, but did not meet the co-primary super-superiority objective of a 10-point margin.

Table 2-2: Primary Efficacy Endpoint (Mean Difference in %EWL) in ITT-LOCF Population at 12 Months

%EWL	VBLOC	Sham Control	Difference
N	162	77	
Mean ± SD	24.4 ± 23.6	15.9 ± 17.7	8.5 ± 21.9
[95% CI]	[20.8, 28.1]	[11.9, 19.9]	[3.1, 13.9]
Super-Superiority P-value			0.71
Superiority P-value			0.002

Greater excess weight loss in the VBLOC group was observed early in the trial. Without adjustment for multiple comparisons, %EWL was significantly higher in the VBLOC over sham control group at every visit after the first month (Figure 2-1).

Figure 2-1: Mean %EWL with 95% Confidence Intervals in ITT Population through 12 Months



The observed %EWL in the VBLOC group was very close to the study design assumption (assumed 25%; observed 24.4%), however the %EWL in the sham control group was underestimated in the design by a factor of three (assumed 5%; observed 15.9%). The level of weight loss observed in the sham control group was approximately four times greater than what has been observed for placebo (non-surgical) controls in obesity trials.[15,16]

Large sham responses have been observed in clinical trials of other medical devices. The reasons for the sham effect observed in the ReCharge trial likely involve the incorporation of a sham surgery as well as a sham device, frequent monitoring and interaction with the device, the impact of the weight management sessions, and the enrollment of a motivated patient population.

Additional Efficacy Results through 18 Months

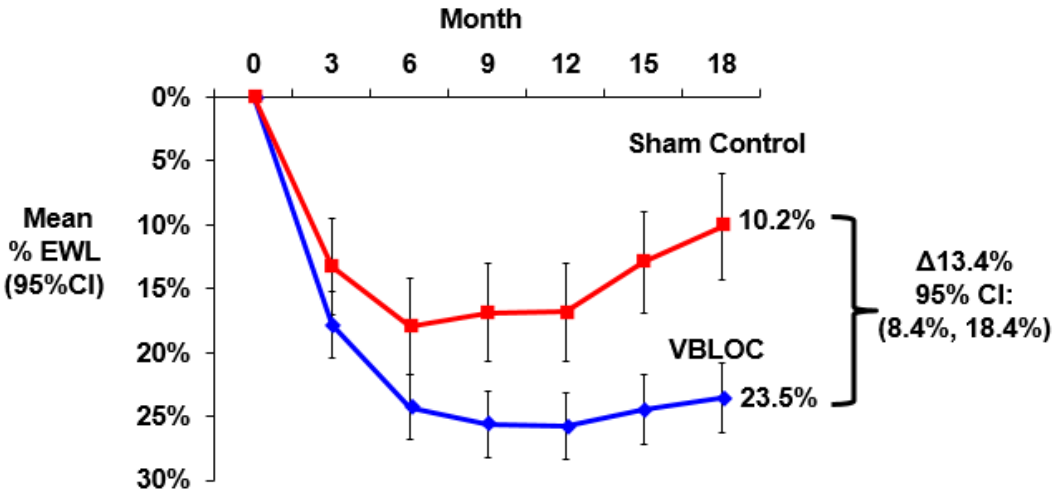
The trial's blind was maintained until all enrolled patients had passed the 12-month follow-up visit and all data had been verified. Due to the rolling nature of enrollment, most patients remained blinded for several months after the 12-month follow-up visit. The median time to unblinding was 16 months for both groups. Specifically, at 15 months, 84% of VBLOC subjects and 90% of sham control subjects (86% total) remained blinded. At 18 months, 27% of VBLOC subjects and 25% of sham control subjects (26% total) remained blinded.

A mixed-effects regression model was used to estimate %EWL through 18 months in order to account for missing data in an ITT analysis (Table 2-3). At 18 months, patients in the VBLOC group largely maintained their weight loss while those in the sham control group regained over 40% of the weight they had lost on average through 12 months. The estimated difference between VBLOC and sham control groups increased from 8.9 percentage points (95% CI: 4.3 to 13.5) at 12 months to 13.4 percentage points (95% CI: 8.4 to 18.4) at 18 months. The fact that the majority of patients were blinded through 16 months is important in the consideration of long-term efficacy data because sham control patients had regained about a quarter of the weight they had lost through 12 months before being unblinded, so the trend of weight regain in the sham group cannot be fully attributed to unblinding of randomization assignments.

Table 2-3: Mixed-Effects Model Estimates for %EWL at 12, 15, and 18 Months

Visit Month	VBLOC Mean [95% CI]	Sham Control Mean [95% CI]	Difference Mean [95% CI]
12 months	25.8% [23.2, 28.4]	16.9% [13.1, 20.7]	8.9 [4.3, 13.5]
15 months	24.4% [21.7, 27.1]	12.9% [9.0, 16.9]	11.5 [6.7, 16.3]
18 months	23.5% [20.8, 26.2]	10.2% [6.0, 14.4]	13.4 [8.4, 18.4]

Figure 2-2: Mixed-Effects Model Estimates for %EWL through 18 Months



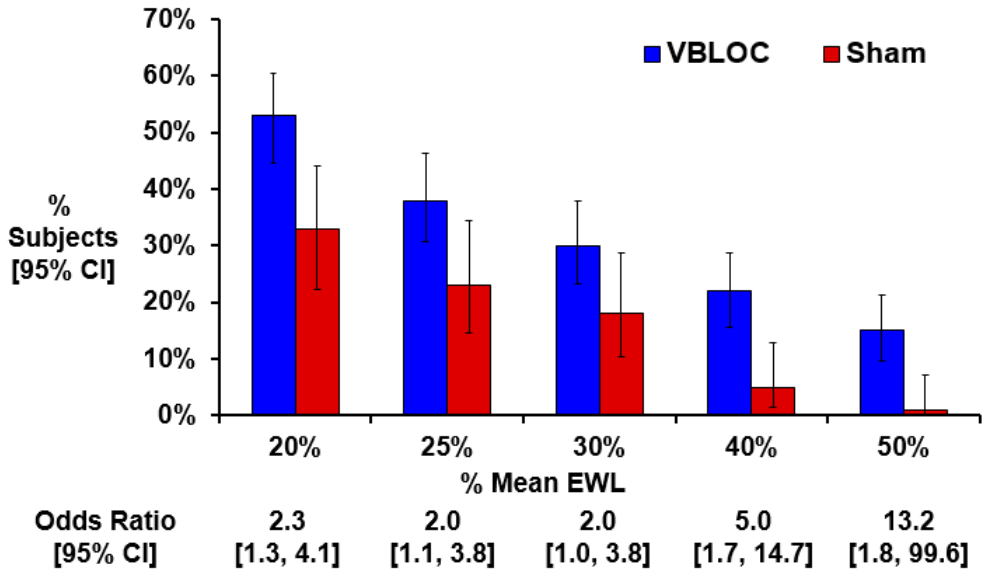
2.6.3.2 Second Co-Primary Efficacy Endpoint

With regard to the second co-primary endpoint, 52.5% of subjects in the VBLOC group achieved at least 20% EWL and 38.3% of subjects achieved at least 25% EWL. The observed proportions did not meet the pre-specified thresholds of 55% and 45%, respectively, so the second co-primary endpoint was not met. However, more than half of the VBLOC subjects achieved 20% EWL, which is considered to be a clinically significant level of weight loss.

2.6.4 %EWL Responder Rates

The %EWL responder analyses for the ITT population through 12 months are summarized in Figure 2-3. Overall, VBLOC patients had greater odds of achieving higher %EWL thresholds than patients in the sham control group at every threshold from 20% to 50% EWL. Importantly, the relative likelihood of a VBLOC patient achieving weight loss thresholds compared to a sham control patient increased as the thresholds became harder to attain.

Figure 2-3: %EWL Responder Rate Analysis in ITT Population at 12 Months



2.6.5 Changes in Quality of Life and Patient Questionnaires

Improvements in quality of life and hunger and appetite measures (i.e., Impact of Weight on Quality of Life-Lite [IWQoL-Lite] and Three Factor Eating Questionnaire [TFEQ]) were observed in both groups commensurate with the weight loss observed. In particular, the improvement in the Hunger factor of the TFEQ was significantly better in the VBLOC group compared to the sham group at 12 months, consistent with the mechanism of action of VBLOC therapy. As described in Sections 4.6.9 and 4.6.10, the improvements for VBLOC remained durable through 18 months while the improvements in the sham control group began to decline. The significance levels for these analyses are unadjusted for multiple comparisons.

2.6.6 Changes in Metabolic, Cardiovascular, and Anthropometric Risk Factors

Supporting analyses were conducted to examine the impact of weight loss on multiple parameters. Statistically significant improvements from baseline were observed for both groups in total cholesterol, LDL, triglycerides, systolic and diastolic blood pressure, heart rate and waist circumference. Detailed results are shown in Table 4-17.

2.6.7 Safety Results

2.6.8 Primary Safety Endpoint

The primary safety endpoint, defined as the proportion of subjects in the VBLOC group who experienced an implant/revision procedure, device, or therapy-related SAE through 12 months post-implant, was 3.7% (95% CI, 1.4% to 7.9%) in the ITT population. This rate was significantly lower than 15% performance goal ($p<0.0001$), so the primary safety endpoint was met. The SAEs included two cases of neuroregulator malfunction and one case each of pain at the neuroregulator site, atelectasis, gallbladder disease, and emesis. There were no deaths, UADEs, or SAEs that typically occur in conventional bariatric procedures, such as stricture, anastomotic leak, or bowel obstruction.

2.6.9 Additional Safety Data

The overall SAE rate, both related and unrelated to treatment, was 13.0% in the VBLOC group and 5.2% in the sham control group. The most common SAE through 12 months was nausea which occurred post-surgery in six VBLOC subjects (3.7%). The majority of SAEs were single instances of events, most of which were deemed to be not related such as chest pain, osteoarthritis, and palpitations. A listing of all SAEs is provided in Table 4-27.

Most AEs were non-serious and were unrelated to the device, procedure, or therapy. Those that were related were generally mild to moderate in intensity and included pain and GI related complaints such as heartburn, dysphagia, belching, and nausea. Importantly, 98% of all related AEs in the VBLOC group in the first 12 months were reported by the investigator to be mild or moderate in severity. A listing of all related AEs through 12 months is shown in Table 4-31.

AEs potentially related to the vagus nerve included heartburn/dyspepsia, nausea, vomiting, eructation, diarrhea, and abdominal pain. These AEs may be side effects of the flow of current from the anode to the cathode through muscle and other tissue during therapy. These symptoms have been described by subjects as transient and are often correlated with time periods when VBLOC therapy is being delivered. The transient nature of the symptoms supports the findings of preclinical studies which demonstrate that there is no injury to the vagus nerve from VBLOC therapy.

Both blood pressure and heart rate were reduced in the VBLOC and sham control groups suggesting that no adverse cardiovascular signal was observed over the first 12 months of the study. In addition, the reduction in heart rate was confirmed by ECGs that were conducted at screening, 4, 8, and 12 months. At each of the three follow-up time points with ECGs, there were no clinically important or statistically significant differences between the two groups for

the important variables of heart rate, PR, QRS and QTcF. There were no ECG findings that suggest any influence on vagal tone or on the cardiac conduction system by the Maestro Rechargeable System.

2.7 BENEFIT/RISK CONCLUSION

The ReCharge Study is a randomized, double-blind, sham controlled trial of VBLOC therapy using the Maestro Rechargeable System. After 12 months of treatment, VBLOC subjects achieved an average 24.4% EWL (9.2% TBL) in the ITT population. The majority of VBLOC subjects achieved a clinically meaningful level of weight loss. At 12 months, 52% of VBLOC subjects achieved at least 20% EWL and 38% had at least 25% EWL. In terms of %TBL, 64% achieved at least 5% TBL, 54% achieved 7% TBL, and 36% achieved 10% TBL.

The ReCharge Study did not meet its efficacy endpoints; however, the VBLOC group demonstrated significantly greater weight loss than the sham control in both average weight loss and in responder analyses of clinically meaningful weight loss thresholds. Most importantly, weight loss for VBLOC patients was shown to be durable through 18 months, while sham control patients regained a large proportion (>40%) of the weight they had lost at 12 months.

Supporting data from the ReCharge Study demonstrate the benefits of the weight loss obtained in the VBLOC group. Significant reductions in obesity-associated risk factors including LDL cholesterol, triglycerides, systolic and diastolic blood pressure, heart rate and waist circumference were observed. Similarly, sustained improvement in IWQoL-Lite and TFEQ scores show that VBLOC has a meaningful effect on quality of life and sensations of hunger. Similar to the weight loss results, these improvements remained durable for VBLOC patients through 18 months but diminished over time in sham control patients.

Data from landmark obesity studies, such as LOOK AHEAD and DPP provide further supporting evidence for the clinical significance of the weight loss achieved in the VBLOC subjects. For example, LOOK AHEAD demonstrated that 8.6% TBL at 12 months was associated with a 15% decrease in the incidence of metabolic syndrome, as well as decreases in blood pressure, use of antihypertensive medications and improvements in hyperlipidemia. DPP showed that 7% TBL at one year resulted in 58% reduction in the development of Type II diabetes in insulin resistant patients.

The majority of the AEs observed in the ReCharge Study were non-serious and many were unrelated to the device, procedure or therapy. Of those events that were related to treatment with VBLOC therapy, 98% were mild to moderate in intensity and most resolved with alterations to the therapy algorithm, medical therapy, or without intervention. The most common related AEs reported were pain and GI symptoms, including heartburn, dysphagia, belching and nausea. There were no AEs to suggest any damage to the vagus nerve. The 12-month primary SAE rate of 3.7%, which was considerably lower than the 15% performance goal, provides evidence for the safety of VBLOC therapy, especially in comparison to current surgical weight loss options. Importantly, no SAEs were observed that are typical for existing bariatric procedures, such as stricture, anastomotic leak, and device erosion.

In conclusion, the ReCharge Study demonstrates an excellent safety profile for the Maestro Rechargeable System with a considerably lower occurrence of major adverse events than conventional bariatric surgeries. Following FDA's new paradigm for obesity devices, this low level of risk allows for a determination that a more modest treatment effect is acceptable.[24] The Maestro Rechargeable System provides safe, durable, and clinically significant weight loss that results in significant improvements in obesity risk factors and quality of life. Considering the lower risk and the unmet public health need for new obesity therapies, the data in this PMA application provide a reasonable assurance that the benefits of the Maestro Rechargeable System for treating morbid obesity clearly outweigh the low risks of treatment.

3 OVERVIEW OF MAESTRO RECHARGEABLE SYSTEM AND CLINICAL DEVELOPMENT

3.1 SUMMARY

- The proposed indication for Maestro Rechargeable System is for weight reduction in adult patients with obesity who have 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 co-morbid conditions, and have failed at least one supervised weight management program within the past five years.

- The Maestro Rechargeable System is comprised of an implantable neuroregulator and leads and external components that are used to recharge the battery and monitor the system. It is designed to deliver VBLOC therapy, which blocks conduction on the anterior and posterior trunks of the intra-abdominal vagus nerve.

- Pre-clinical studies evaluated the safety of VBLOC therapy and the effect on nerve and target organ function. The studies show that application of 5000 Hz with VBLOC therapy inhibits pancreatic secretions and gastric contractions and inhibits action potential propagation, but is reversible and safe. The previous EMPOWER and VBLOC-DM2 clinical studies affirmed significant weight loss at 12 months that was sustained with longer-term use. A low rate of procedure, device, or therapy-related SAEs demonstrated safety and supported the initiation of a more definitive pivotal study of the current device model.

- The ReCharge Study is a randomized, double-blind, sham-controlled trial of 239 subjects conducted at 10 investigational sites to evaluate the safety and effectiveness of the Maestro Rechargeable System.

3.2 OVERVIEW OF MAESTRO RECHARGEABLE SYSTEM

The Maestro Rechargeable System delivers electrical blocking signals to the anterior and posterior trunks of the intra-abdominal vagus nerve. The Maestro Rechargeable System consists of implanted and external components (Figure 3-1, Figure 3-2). Internal components include a rechargeable neuroregulator and two flexible leads, which connect the neuroregulator to the electrodes placed around the vagus nerve. The placement of the flexible electrode leads are to the anterior and posterior trunks (Figure 3-3).

Figure 3-1: Components of Maestro Rechargeable System

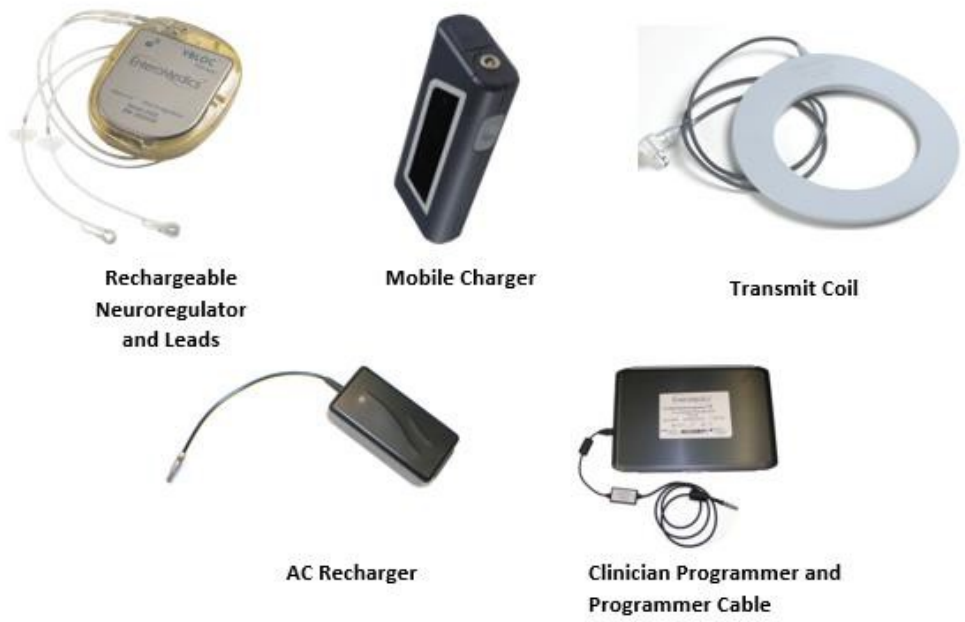
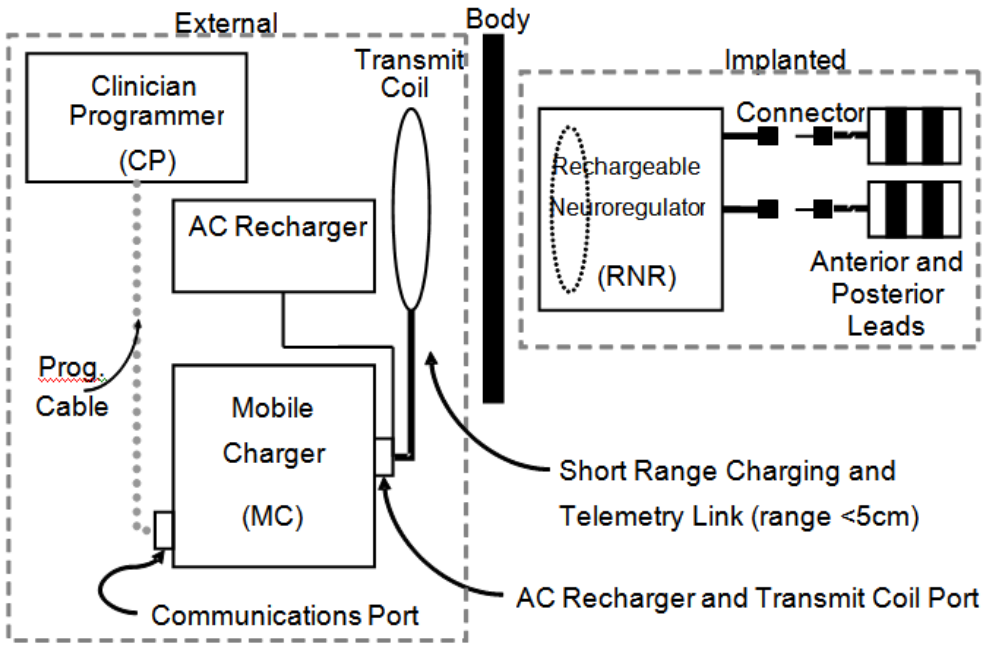


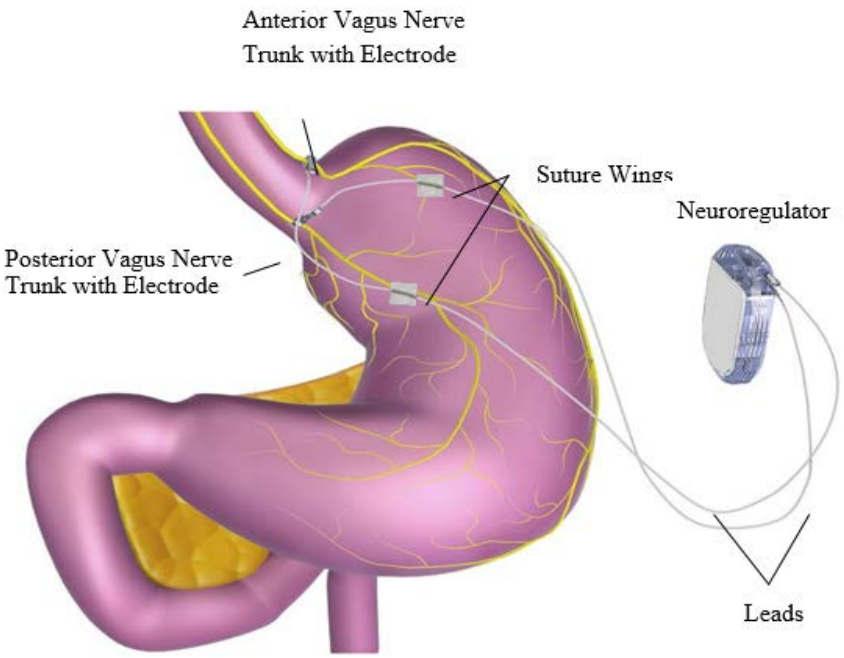
Figure 3-2: Illustration of Implanted and External Components of the Maestro Rechargeable System



External components include a clinical programmer, programmer cable, mobile charger, transmit coil, and AC recharger. The mobile charger and transmit coil are used to check the charge level in the neuroregulator battery and recharge the battery when necessary. The AC Recharger is used to charge the internal battery of the mobile charger. The clinician programmer is used during surgery and follow-up. It consists of a commercially available

laptop computer with a proprietary software program that communicates with the mobile charger and neuroregulator. It allows clinicians to modify therapy parameters and to retrieve diagnostic information.

Figure 3-3: Maestro Rechargeable System Placement



The Maestro rechargeable neuroregulator is sterile and consists of a hermetic case enclosure containing the battery and electronic circuitry surrounded by a header with an integrated coil that acts as the telemetry and recharging antenna. The header/coil assembly uses one set screw for connection and fixation of each lead.

The battery is an internal 2.6 AH Li-ion rechargeable battery that has been used in implantable medical devices since 1999. The battery is recharged transcutaneously using the transmit coil. The patient is instructed to recharge daily until the battery indicator on the mobile charger shows that the neuroregulator battery is fully charged. Recharging takes approximately 30 minutes, depending on the degree of discharge of the battery.

The mobile charger and neuroregulator are designed to transfer energy and information solely between each other, up to a maximum distance of 5 cm.

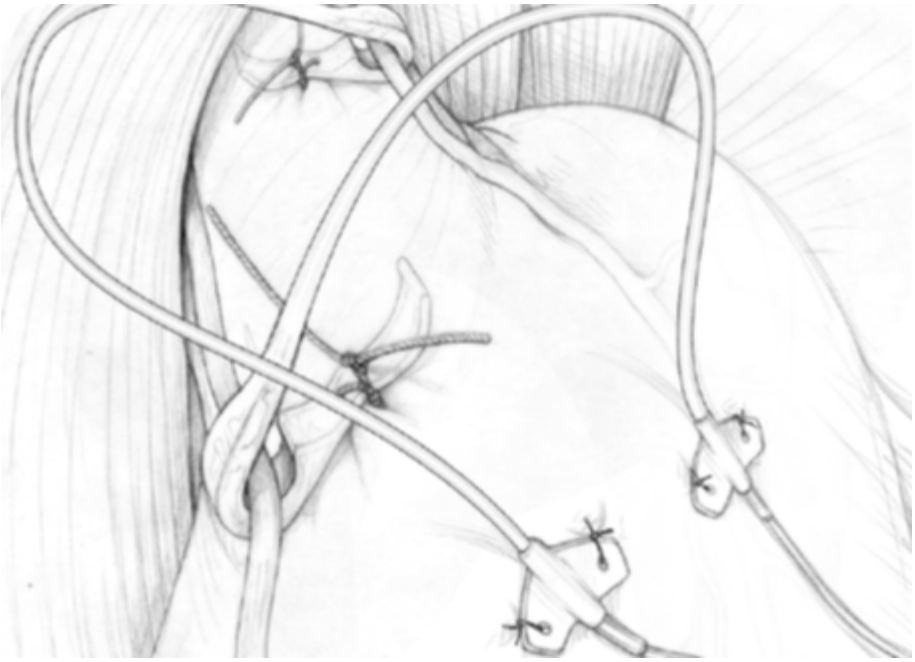
3.3 PLACEMENT OF THE MAESTRO RECHARGEABLE SYSTEM LEADS

The rechargeable neuroregulator is placed subcutaneously on the lower chest region in the area slightly anterior to the axial line and caudal to the axilla. The leads are implanted laparoscopically and cradle the vagus nerve at the gastroesophageal junction and the rechargeable neuroregulator is implanted in a subcutaneous pocket. Two sterile bipolar leads are implanted: one lead for the anterior vagal nerve trunk and one lead for the posterior vagal nerve trunk.

The lead electrodes are placed in contact with the appropriate vagal trunk. During the lead implantation procedure, the surgeon grasps the lead and electrode by the suture tongue. The suture tongue is manipulated to guide the electrode into place. The electrode is then anchored in a position such that the nerve-electrode contact is maximized. The electrode is not secured to the nerve, but is anchored to the esophagus by the surgeon placing a suture through the superficial muscular layer of the esophagus and then through the suture hole in the suture tongue (Figure 3-4). A non-absorbable suture is recommended for secure attachment. No clips are used. No compression of the nerve is experienced as the electrode is of an open design and no suturing is done to the nerve. Strain relief is provided by placing two additional sutures through the suture wings along the lead in the seromuscular layer of the stomach.

The neuroregulator is implanted between 2 to 3 cm deep under the skin with the flat side of the neuroregulator approximately parallel to the skin surface. Implantation at this depth produces optimal charging and telemetry link between the transmit coil and the neuroregulator.

Figure 3-4: Intra-Abdominal Lead Placement



3.4 BENCH TESTING

The Maestro Rechargeable System was developed in accordance with design controls and a risk management process that conformed to ISO 14971:2009 to identify and manage Maestro Rechargeable System hazards and risks. All components were evaluated and met performance criteria. Software was developed, verified and validated, and met software specified requirements.

The Maestro Rechargeable System was tested at the system level by verifying the functionality in each of the typical system use cases; in the operating room during implantation, in the clinic for patient follow up, patient use, and recharging of the mobile charger and neuroregulator.

Default system settings and settings access were also tested. Finally, a comparison of the waveform morphology between the Maestro RF2, the previous generation of the device that was not fully implantable, and Maestro Rechargeable System was performed to verify that the waveforms match, verifying the animal study safety testing performed using the Maestro RF2 System is applicable to the Maestro Rechargeable System. The Maestro RF2 System utilized the same leads as the Maestro Rechargeable System, however, the external components included a battery-powered external controller connected to a cutaneous transmit coil that is positioned over the implanted neuroregulator.

Biocompatibility of the implantable portions of the Maestro Rechargeable System was tested in accordance with ISO 10993-1:2009. All implanted, tissue-contacting materials have a long history of use in other implanted devices and all passed the required tests.

Shelf life, packaging validation tests, and sterilization validation tests were successfully completed per industry standard practices and internationally recognized standards. Components were sterilized by ethylene oxide with a sterility assurance level of 10^{-6}. Shelf life for the rechargeable neuroregulator has been established as 18 months from the date of sterile packaging. Shelf life for the anterior and posterior leads has been established as 36 months from the date of sterile packaging.

3.5 REGULATORY HISTORY

EnteroMedics submitted an application for Premarket Approval to the FDA in June 2013 proposing the following indication:

- *The Maestro Rechargeable System is indicated for use in weight reduction in adult patients with obesity who have a Body Mass Index (BMI) of at least 40 kg/m^2, or a BMI of at least 35 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.*

During development of the Maestro system, EnteroMedics and FDA discussed clinical development. Key meetings and regulatory actions are listed below. All FDA issues and concerns have been satisfactorily addressed:

- June 2007: Initial IDE approval for EMPOWER clinical study (G070025/S002)
- January 2010: FDA meeting to discuss EMPOWER study results and ReCharge clinical trial design
- March 2010: Supplemental IDE submitted for ReCharge clinical trial utilizing the Maestro Rechargeable System
- July 2010: Initial conditional approval for ReCharge clinical trial utilizing the Maestro Rechargeable System
- May 2011: First ReCharge clinical trial subject implanted
- July 2011: CE marking obtained for Maestro Rechargeable System

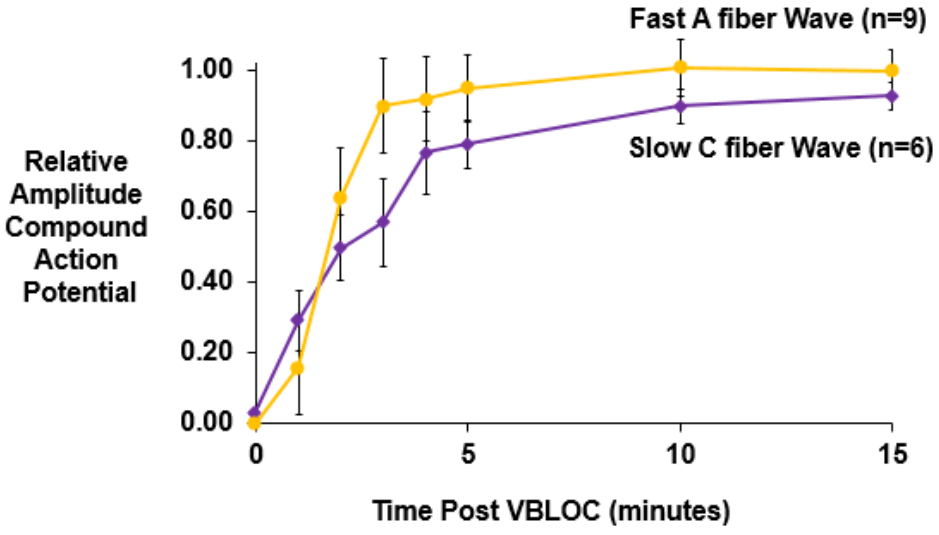
- December 2011: Final ReCharge clinical trial subject implanted
- January 2013: Final ReCharge clinical trial subject 12-month follow-up completed
- May 2013: Pre-PMA meeting with FDA review team
- June 2013: PMA submitted to FDA
- October 2013: Day 100 meeting with FDA review team
- November 2013: Submission of PMA amendment with additional information

3.6 PRE-CLINICAL ANIMAL STUDIES

Pre-clinical studies evaluated vagal nerve blocking therapy for safety and to determine the appropriate algorithm to initially evaluate in humans. The studies show that application of 5000 Hz (VBLOC therapy) inhibits action potential propagation, pancreatic secretions, and gastric contractions, but is reversible and does not adversely affect axonal function or nerve histopathology.

A rat model was used to understand how applying 5000 Hz to the vagal nerves affected compound action potential (CAP) propagation or nerve conduction. In a study of 9 rats, 5000 Hz was applied for 5 minutes which resulted in a complete inhibition of CAP propagation. Removing the block allowed the nerve to recover after about 5 minutes which demonstrates that the blocking is reversible (Figure 3-5).

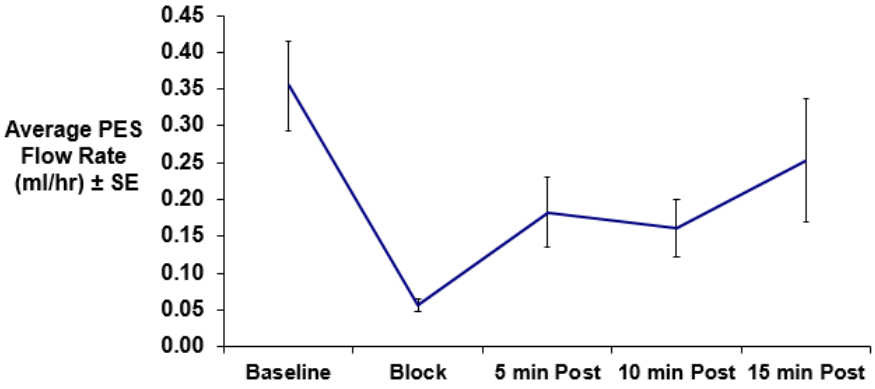
Figure 3-5: Results of Nerve Function Study of VBLOC in Rodent Model



The juvenile porcine pancreatic exocrine section model was used to understand how high frequency algorithms applied to the abdominal vagal trunks affects GI organ function. This model utilizes juvenile pigs that are fasted for 18 hours. A 5000 Hz signal was then applied to

the intra-abdominal vagal trunks for 5 minutes which resulted in more than 80% reduction in the flow rate of pancreatic exocrine secretion, a statistically significant difference from baseline in the five pigs tested (p=0.005). As shown in Figure 3-6, when block was discontinued, PES flow rate was 75% recovered by about 15 minutes post-block.

Figure 3-6: Pancreatic Exocrine Secretion Flow Rate after VBLOC in Juvenile Porcine Model



The same juvenile pig model was used to understand how 12 Hz, which is a stimulating frequency, and 5000 Hz, which is a blocking frequency, applied to the abdominal vagal trunks affected gastric contractions relative to baseline. In this study, three pigs were used and they had a baseline contraction frequency of 5.6 ± 1.1 contractions per minute. Relative to baseline, when VBLOC therapy was applied (5000 Hz, 6 mA), the contractions were reduced by about 80%, to 1.2 ± 0.3 contractions per minute. However, when stimulating parameters are applied (12 Hz, 6 mA) the stomach contractions were shown to increase by approximately the same 80% amount. This suggests that VBLOC therapy causes a relative decrease in gastric motility.

Before first use in humans, pre-clinical studies of vagal nerve blocking therapy were performed in a porcine model using 71 animals. The algorithm used in the studies consisted of 5000 Hz, up to 8 mA, 0.09 msec pulse width for 5 minutes “on” followed by 5 minutes “off” up to 24 hours per day. These studies demonstrated the following:

- 91-98% of axons were normal using axonal analysis.
- There was no evidence of necrosis or Wallerian degeneration.
- Some isolated early-stage axonal degeneration accompanied by swelling was observed. We interpret these instances as transient, since regenerating axons without inflammatory signs were observed in the same tissue samples. These changes were attributed to limitations of the animal model due to exteriorization of the leads and natural growth of the animals. Of note, the relatively mild nature of the vagally-mediated adverse events seen in multiple human studies of VBLOC therapy support this conclusion.
- Cumulative histology was primarily normal fascicles.

- Fibrous capsule developed between electrode and vagus nerve was complete by 12 weeks using fibrous capsule measurements.

- Organs innervated by the vagus nerve were not adversely affected by VBLOC therapy. Organs evaluated included stomach, pancreas, gall bladder, liver and brain.

- Conduction velocities after 12-79 days of vagal nerve blocking were consistent with those reported in the literature when controlling for similar methods and temperatures.

3.7 CLINICAL MECHANISM OF ACTION STUDIES

Clinical mechanism of action studies were performed in humans to assess calorie intake and dietary composition, inhibition of plasma pancreatic polypeptide and maximum tolerated volume. These studies show that, compared to baseline, chronic delivery of VBLOC therapy results in a reduction in food intake, inhibition of plasma pancreatic polypeptide (PP), and a reduction in maximum tolerated volume (MTV) ingested.

Calorie Intake and Diet Composition Study *(Wray et al., 2011)* [25]

Ten patients (6 females) with a mean BMI of 38 kg/m^2 were implanted at one center in Australia with the Maestro Rechargeable System and received VBLOC Therapy for 12 months. Seven-day diet diaries were taken at pre-implant and after 1, 3, 6, and 12 months of VBLOC therapy to quantify changes in calorie intake and dietary composition. Each diet diary was verified during a detailed interview with a nutritionist. A validated program for determining nutrient and calorie content in food was used to quantify as percent of total the amount of intake from carbohydrates, fat, and protein. Dietary composition expressed as percent fat, carbohydrate and protein in the daily intake was essentially unchanged throughout the follow-up period. Calorie intake decreased significantly from baseline intake of 2062 kcal/day by 45%, 48% , 37%, and 30%, respectively, at 1, 3, 6, and 12 months.

Plasma Pancreatic Polypeptide Study *(Camilleri et al., 2008)*[26]

Twenty-five patients (20 females, BMI: 33 to 48 kg/m^2) at two OUS centers underwent sham feeding before implant and after 12 weeks of VBLOC therapy with the Maestro RF System. Plasma pancreatic polypeptide (PP) response to sham feeding was used as a noninvasive test of vagal efferent function. Plasma PP levels were obtained in fasted patients at baseline and throughout a 20 minute sham feeding. Patients avoided swallowing food or saliva to eliminate the nutrient activation of pancreatic secretion. Before Maestro System implant, sham feeding resulted in normal plasma PP response with increases above baseline of at least 25 pg/mL (mean plasma PP above baseline at 20 minutes, 42 ± 19 pg/mL). Following 12 weeks of VBLOC therapy, plasma PP responses at 20 min were suppressed (mean plasma PP above baseline at 20 minutes, 20 ± 7 pg/mL).

Maximum Tolerated Volume Study *(Herrera et al., 2009)*[27]

Eight subjects (5 females; mean BMI 40 kg/m^2) were implanted with the Maestro RF System in an open-label study at one OUS center. Subjects underwent standardized nutrient drink

tests at baseline and after at least 12 months of VBLOC therapy. At each evaluation, subjects ingested Ensure® (1 kcal/ml) in 120 mL volumes separated by 4-minute intervals until maximum tolerated satiation. Maximum tolerated volume (MTV) was calculated as total volume ingested. The baseline MTV of 1383 ± 161 mL was significantly reduced by 246 ± 122 mL at follow-up (p=0.05), representing a mean decrease of 18% in ingested volume at satiation.

3.8 PRIOR CLINICAL STUDY: EMPOWER

EMPOWER was a randomized, double-blind controlled trial of the previous system design, the Maestro RF2 System, which was not fully implantable. The Maestro RF2 System utilized the same leads as the Maestro Rechargeable System, however, the external components included a battery-powered external controller connected to a cutaneous transmit coil that is positioned over the implanted neuroregulator.

Because the external controller holds the external battery, subjects were required to position the transmit coil over the implanted neuroregulator in order for VBLOC therapy to be delivered. Subjects were instructed to wear the external battery for 9 to 16 hours per day. Although subjects were encouraged by the study investigators and coordinators to wear the device as much as possible, the decision to wear the device was solely under the patient's control, and therefore, the patients determined how much therapy was delivered per day.

Subjects randomized to VBLOC therapy had their devices programmed to deliver therapy at 5000 Hz. Control subjects had their devices programmed to deliver 0 mA of current at 5000 Hz, however some current was delivered throughout each day to perform required impedance and safety checks.

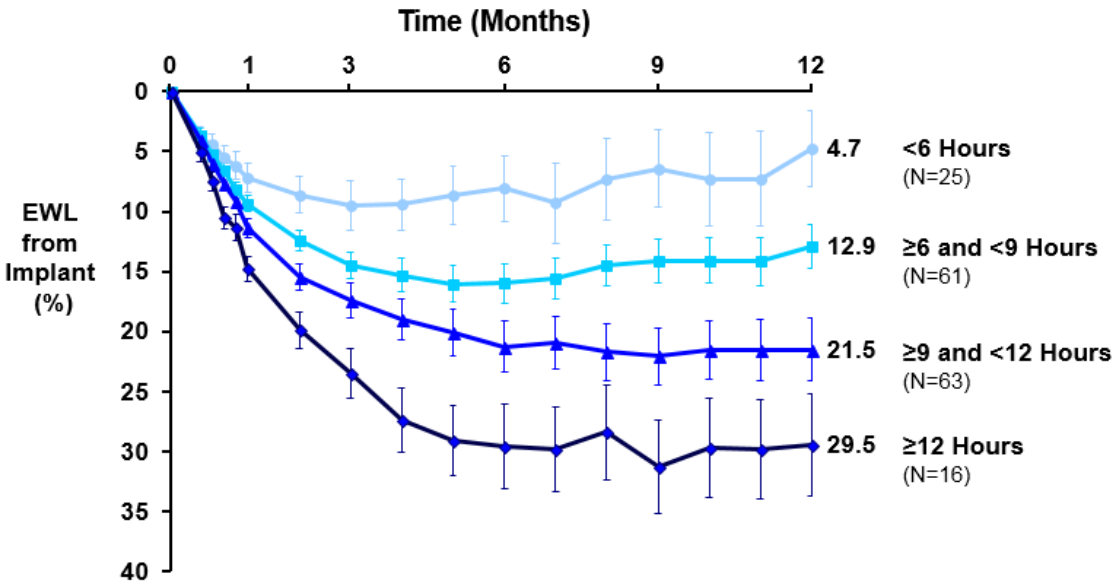
Two hundred ninety four (294) subjects were enrolled and implanted. Subjects had a mean age of 46 years, 90% were Caucasian, and 89% were female. The mean BMI at implant was 41.1 ± 2.7 kg/m^2.

3.8.1 Effectiveness

The primary efficacy endpoint in EMPOWER was not met (approximately 12% EWL by MetLife method was observed in both groups). The primary efficacy objective was to demonstrate super-superiority of treatment over control at a margin of 10 percentage points. Unlike the ReCharge study, the primary endpoint for the EMPOWER study was assessed using the MetLife calculation of %EWL.

There were no differences observed between treatment arms in average hours of therapy per day or therapy algorithm settings. However, both average hours of use per day and total therapy days showed statistically significant positive associations with %EWL from baseline (Figure 3-7). This finding was observed regardless of treatment arm, although there appeared to be a trend towards greater weight loss in the treatment group when the device was worn for ≥12 hours, where the %EWL (BMI method) in the treatment subjects was nearly 30%.

Figure 3-7: EMPOWER Mean %EWL (BMI method) by Average Hours of Use per Day at 12 Months in Treatment Group



EMPOWER was designed as a 5-year study and follow-up is available through 48 months. After the 12-month blinded portion of the trial, all subjects began to receive VBLOC therapy. Interpretation of EMPOWER efficacy data is problematic due to subjects being able to control therapy by whether or not they wore the external battery, therefore safety results are presented overall (among all treatment and control subjects who continued in the trial receiving active VBLOC therapy) and efficacy among treatment subjects who were compliant in the first 12 months of the study (i.e., who wore the device for ≥9 hours on average per day, as recommended in the trial). The weight loss as observed in EMPOWER treatment subjects with ≥9 average hours use was 23.1%, 24.2%, 20.4%, and 18.7% EWL at 12, 24, 36, and 48 months, respectively.

3.8.2 Safety

A blinded Clinical Event Committee (CEC) reviewed and adjudicated all serious adverse events (SAEs). A blinded Data and Safety Monitoring Board (DSMB) reviewed the trial on an ongoing basis.

The DSMB reviewed aggregated clinical laboratory and electrocardiographic data and concluded that there were no findings of clinical significance or concern. No changes in intra-cardiac conduction (PR interval, QRS duration), ventricular repolarization (QTcF interval) or ventricular arrhythmias were associated with either the treatment or control groups in EMPOWER.

Long-term safety beyond 12 months in the EMPOWER Study supports the safety profile of the Maestro Rechargeable System. Through 48 months of follow-up, there have been no deaths or UADEs. Ninety-one (91) SAEs occurred through 48 months. Sixteen (16) SAEs were adjudicated by the CEC as related to implant/revision procedure (6), device (9) or therapy (1). These included pain at the neuroregulator site, device malfunction, pocket

infection, small bowel obstruction, gallbladder disease, headache, abdominal pain and incision pain. The Kaplan-Meier estimates for the related SAE rate are given in Table 3-1.

Table 3-1: EMPOWER Kaplan-Meier SAE Rates through 48 Months

Time Point	Related SAE Rate (N at risk)
12 months	3.1% (276)
24 months	4.2% (216)
36 months	5.7% (140)
48 months	6.5% (89)

The AEs that occurred through 48 months in at least 5% of subjects in either treatment group are shown in Table 3-2. The most common AEs in both groups were pain at the neuroregulator site and heartburn/dyspepsia.

Table 3-2: EMPOWER Related AEs Occurring in ≥5% of Subjects through 48 Months

AE Type	Treatment		Control*	
	N subjects (%)	N events	N subjects (%)	N events
Pain, neuroregulator site	56 (29.2%)	67	31 (30.4%)	34
Heartburn/dyspepsia	46 (24.0%)	54	17 (16.7%)	19
Pain, other (specify)	35 (18.2%)	43	12 (11.8%)	19
Other	36 (18.8%)	39	17 (16.7%)	20
Pain, abdominal	33 (17.2%)	37	20 (19.6%)	25
Nausea	23 (12.0%)	27	8 (7.8%)	8
Skin reaction to coil	21 (10.9%)	26	13 (12.7%)	15
Eructation (Belching)	19 (9.9%)	21	12 (11.8%)	13
Constipation	19 (9.9%)	20	10 (9.8%)	11
Chest pain	17 (8.9%)	18	3 (2.9%)	3
Wound redness or irritation	13 (6.8%)	13	4 (3.9%)	5
Diarrhea	9 (4.7%)	10	8 (7.8%)	9

*Note that control subjects were activated and began receiving VBLOC therapy at the end of the 12-month visit.

3.8.3 Summary of EMPOWER Findings

- At 12 months, the mean %EWL (BMI method) from implant was 16.6% treated (n=165) versus 16.4% control (n=88) with all evaluable subjects regardless of compliance (hours of device use).

- Weight loss was greater with greater hours of device use per day regardless of the treatment arm:

- Mean %EWL (BMI method) from implant was 23.1% (n=79) in the VBLOC group and 22.9% (n=49) in the control group at 12 months for subjects who used the device ≥9 hours per day.
- A trend to increased efficacy in the treatment arm as compared to the control arm at ≥12 hours of device use per day was observed.

- Analysis of the EMPOWER Study results are confounded by the observed variability in hours of device use and potentially by an unanticipated indication of efficacy of control group parameters related to delivery of charge to the vagal nerve from the required device safety checks and diagnostics.
- There were no deaths or UADEs in the EMPOWER study. The Kaplan-Meier SAE rate related to device, procedure, or therapy at 48 months is 6.5%.

3.9 PRIOR CLINICAL STUDY: VBLOC-DM2

VBLOC-DM2 was a pilot study of the Maestro Rechargeable System conducted in obese subjects with type 2 diabetes. The study enrolled 28 subjects into an open label, single-arm, multi-center trial at 5 centers outside the United States.

3.9.1 Effectiveness

The mean weight loss at 12 months was 24.5% EWL. At 12 months, HbA1c dropped 1.0 ± 1% from a mean 7.8% at baseline ($p<0.001$) and fasting glucose declined 28 ± 42 mg/dl from a mean of 151 mg/dl at baseline ($p=0.003$).

Long-term weight loss was evaluated using a mixed-effects regression model to account for missing data. The estimated mean %EWL is shown in Table 3-3.

Table 3-3: VBLOC-DM2 Mean %EWL from Mixed-Effects Model through 36 Months

Visit Month	Mean %EWL [95% CI]
12 Months	24.0% [18.0, 30.1]
18 Months	21.8% [15.6, 28.0]
24 Months	21.8% [15.4, 28.1]
36 Months	20.9% [14.3, 27.6]

3.9.2 Safety

In VBLOC-DM2, there have been no deaths or UADEs. Three (3) device or implant-related SAEs have been reported through 36 months. The Kaplan-Meier rates of device, implant/revision procedure, or therapy-related SAEs at yearly visits are shown in Table 3-4.

Table 3-4: VBLOC-DM2 Kaplan-Meier Related SAE Rates through 36 Months

Time Point	Related SAE Rate (N at risk)
12 months	3.5% (27)
24 months	4.8% (25)
36 months	4.8% (20)

Table 3-5 lists AEs related to device or procedure that occurred in greater than 5% of patients. Heartburn and constipation occur the most frequently among subjects. The pattern was generally similar to what has been observed in the ReCharge and EMPOWER studies.

Table 3-5: VBLOC-DM2 Related AEs Occurring in ≥5% of Subjects through 36 Months

AE Type	N (%) patients	N events
Heartburn	8 (28.6%)	8
Constipation	6 (21.4%)	7
Other	4 (14.3%)	6
Pain, neuroregulator site	5 (17.9%)	6
Nausea	3 (10.7%)	5
Pain	3 (10.7%)	4
Abdominal pain	2 (7.1%)	3
Abdominal cramps	2 (7.1%)	2
Chest pain	2 (7.1%)	2
Wound redness or irritation, neuroregulator site	2 (7.1%)	2
Wound redness or irritation, trocar site	2 (7.1%)	2

3.9.3 Summary of VBLOC-DM2 Findings

- Mean %EWL through 12 months was 24.5% (n=26), which demonstrated that the compliance issues that resulted in lower than expected weight loss in EMPOWER using the RF-2 system had been resolved with the Maestro Rechargeable System.
- Weight loss was largely sustained through 36 months. The estimated %EWL at 36 months was 20.9% (95% CI: 14.3 to 27.6).
- Weight loss was accompanied by improvements in glycemic control.
- The AE profile for VBLOC therapy was consistent with what was observed in the EMPOWER Study.
- There were no deaths or UADEs in the VBLOC-DM2 Study. The estimated SAE rate related to device, implant/revision procedure, or therapy through 36 months is 4.8%.

4 RECHARGE STUDY

4.1 SUMMARY OF EFFECTIVENESS

- In the ITT population at 12 months, the VBLOC group achieved a mean 24.4% EWL, which was significantly greater than the 15.9% EWL in the sham control group, but did not meet the primary endpoint 10-point superiority margin. The sham control response was three times greater than anticipated in the study design.

- In the ITT population at 12 months, 52.5% of VBLOC subjects achieved at least a clinically relevant 20% EWL and 38.3% achieved at least 25% EWL, which were lower than the respective 55% and 45% pre-specified targets. In the ITT population, 55% of VBLOC subjects achieved at least 18% EWL and 45% achieved at least 23% EWL.

- In the per-protocol population, the mean %EWL was 26.3% in the VBLOC group and 17.3% in the sham control group. In the per-protocol population, 56.8% of VBLOC subjects achieved at least 20% EWL and 41.8% achieved at least 25% EWL, which met one of the responder endpoint targets.

- Weight loss in the VBLOC group was maintained through 18 months with a mean 23.5% EWL while sham control subjects had regained 40% of their 12 month weight loss with a mean 10.1% EWL. Most of the weight regain in the sham control group through 18 months preceded unblinding.

- Cardiovascular and metabolic risk factors and quality of life measures were not pre-defined endpoints, but were assessed throughout the study for their clinical relevance. Significant improvements from baseline were observed in both groups at 12 months, commensurate with the weight loss achieved. Differences between groups were not significant with the exception of sensations of hunger. Similar to weight loss, improvements for the VBLOC group were sustained at 18 months while the sham control group improvements were diminished.

4.2 STUDY DESIGN

ReCharge was a randomized, double-blind, sham-controlled trial designed to evaluate the safety and efficacy of the Maestro Rechargeable System. Subjects were randomized in a 2:1 allocation ratio to VBLOC therapy with the Maestro Rechargeable System or sham surgical control. Subjects were enrolled with a BMI 40 kg/m^2 to 45 kg/m^2 or BMI 35 kg/m^2 to 39.9 kg/m^2 with at least one obesity related co-morbid condition. Subjects with type 2 diabetes were limited to 10% of randomized subjects, with no more than 3 subjects enrolled per center. All enrolled subjects participated in a weight management program, which provided recommendations regarding diet, exercise, and behavior modification throughout the study.

Subjects, investigators, coordinators and weight management personnel were blinded to randomization assignment until all subjects had completed 12 months of follow-up and endpoint data were confirmed. As a result, the blind was maintained for several months after the 12 month follow-up visit. The median time to unblinding was 16 months for both groups. Sponsors' company management, clinical management, engineering management, and regulatory groups were also blind to randomization assignment until all subjects had completed 12 months of follow-up. Personnel unblinded to randomization assignment included the implanting surgeon and operating room team, an unblinded statistician, and specific sponsor personnel needed to support the safe use of the device and to monitor the clinical trial conduct.

Unlike other weight loss device studies, the sham control group received a sham procedure designed to replicate the procedure used to implant the Maestro Rechargeable System. The sham control subjects received general anesthesia and were implanted with a functional sham neuroregulator but no leads to the vagus nerve. The sham neuroregulator was designed using resistors that dissipate charge in a manner similar to the active neuroregulator. The battery in the sham device depleted in the same fashion as the Maestro Rechargeable System and interfaced with the clinical programmer and mobile charger in the same way. To replicate the placement of leads, control subjects had up to five small incisions created through the skin layer only, to simulate placement of 5 mm trocars. Both VBLOC and sham control subjects, therefore, had the same number of incisions following surgery and had to monitor and recharge their devices with the same frequency. Thus, the sham control group had a very similar experience as subjects receiving the Maestro Rechargeable System in the VBLOC group.

Following unblinding, sham control subjects have the option to cross-over and receive a fully functioning Maestro Rechargeable system, including lead placement on the vagal trunks. As of September 11th, 12 subjects had crossed over to receive an active device.

4.2.1 Device Settings

Based upon the pre-clinical data described above, clinical studies used the following parameters for therapy: frequency of 5000 Hz, amplitude of 1 to 8 mA with a target of 6 mA, and pulse width of 0.09 msec. These parameters were established through safety and proof-of-concept efficacy studies using porcine and rodent models and were used in the earlier EMPOWER and VBLOC DM-2 trials.

In the Maestro Rechargeable System, the amplitude is programmable by the clinician. In the clinical studies, the objective was to deliver the maximum amplitude tolerable by the subjects (up to 6 mA through the 6-month visit). To minimize the possibility of AEs that could be related to blocking the vagus nerve, the therapeutic algorithm was designed with three levels of intermittency. Specifically, electrical blocking signals are only produced during the waking hours of the subject with an average of 13 hours on time and 11 hours off time. The algorithm during the 13 hours on time is programmed for five minutes "on" followed by five minutes "off." During the 5-minute "on" cycle the device is programmed for a one-minute "off" period in between two, two-minute "on" periods. This algorithm is repeated every 10 minutes for the full time of therapy.

At the time of implantation, devices were set to an amplitude of 1 mA with a treatment schedule of 13 hours per day. For all subjects, the amplitude was increased to 3 mA at the 1-week visit and was increased by 1 mA each following week with a goal of reaching 6 mA at the 4-week visit. The systematic amplitude increases were performed for both VBLOC and sham control groups to maintain blinding. Subjects who could not tolerate 3 mA at the 1-week visit or a 1 mA incremental increase at any visit were increased at a slower rate and/or smaller increments. Therapy at 6 mA (or maximal tolerated amplitude) and 13-hour delivery schedule per day were to be maintained for the remainder of the first 6 months (Figure 4-1). Note that 13 hours of therapy was programmed to achieve a minimum of 12 hours of therapy per day to allow time for daily battery recharging, during which therapy is not delivered.

Figure 4-1: Schematic of Therapy Programming for ReCharge Subjects

	Therapy Level	Duration of Therapy (hours per day)
Initial Setting	1 mA	13 Hours/day
Week 1	3 mA	13 Hours/day
Week 2	4 mA	13 Hours/day
Week 3	5 mA	13 Hours/day
Week 4	6 mA	13 Hours/day

Beyond the 6-month visit, the therapy settings were left unchanged if the subject was losing weight and was not experiencing unacceptable AEs. If a subject was not losing weight at an expected rate or was experiencing unacceptable AEs, the therapy settings were adjusted up or down (to a maximum of 8 mA at 13 hours per day). The therapy settings for all subjects were adjusted by a blinded coordinator. Once the maximum tolerated amplitude was attained, further therapy could be delivered by increasing the hours of delivery per day up to 18 hours per day.

4.2.2 Weight Management Program

The weight management program utilized during the ReCharge Study was the same program as was used in the EMPOWER Study. All subjects in both treatment groups participated in the program. In total, each patient was scheduled for 17 face-to-face sessions through the first 12 months of the study. The first session was 45 minutes, sessions 2-4 were 30 minutes, and the remaining sessions were 15 minutes (Table 4-1).

Table 4-1: Visit Schedule for Weight Management Program

Visit	Visit Duration
Visit 1	45 minutes
Visits 2-4	30 minutes
Visits 5-17	15 minutes

The weight management counseling was done by the blinded study coordinator or by the blinded site nutritionist. The weight management program consisted of educational sessions on topics including healthy food choices, physical fitness, mindful eating, handling stress, eating outside the home. The weight management program did not include intensive interventions such as very low calorie diets, portion controlled meals, mandatory exercise programs, or the use of weight loss pharmacotherapy. Prior to implant, at weeks 1-4, and once per month during the first year of the study, the subjects completed a 7-day diet and exercise diary.

4.2.3 Adjudication of SAEs

All SAEs in ReCharge were adjudicated by an independent CEC. The CEC was composed of five members with expertise in bariatric surgery, endocrinology, gastroenterology and biostatistics. The CEC met as needed during the first 12 months of the study to adjudicate SAEs primarily in a blinded manner. Review of individual events that involved x-rays resulted in necessary unblinding of that event due to lead placement in VBLOC subjects only. The CEC adjudicated relatedness of events into the following categories:

- **Device:** An adverse event related to presence of the device, failure of the device to deliver therapy, delivery of electrical impulses outside programmed settings, or other device failure or malfunction

- **Therapy algorithm:** An adverse event related to a delivery of therapy as programmed

- **Implant or Revision Procedure:** An adverse event related to the Maestro System implant or revision procedure (e.g., infection at the neuroregulator site)

- **General Surgical Procedure:** An adverse event related to an aspect of the general surgical procedure (e.g., anesthesia administration) but not to the Maestro System per se

- **Pre-existing Condition:** An adverse event related to an injury or health condition that was known or existed prior to the study (e.g., hypertension)

- **Not related/Other:** An adverse event that could not be classified in one of the other categories

4.2.4 Inclusion Criteria

1. Informed consent

2. Body mass index (BMI) 40 kg/m^2 to 45 kg/m^2 or BMI 35 kg/m^2 to 39.9 kg/m^2 with at least one obesity related co-morbid condition. Co-morbid conditions may include one or more of the following and will be documented on the appropriate case report form:

    - Type 2 diabetes mellitus as defined in inclusion criterion #3 (limited to 10% of randomized subjects)

    - Hypertension as defined by systolic pressure > 140 mm Hg and/or diastolic pressure >90 mm Hg

    - Treated or untreated with systolic ≥140 mmHg and/or diastolic pressure >90 mm Hg

    - Treated with systolic <140 mm Hg and/or diastolic <90 mm Hg

    - Dyslipidemia as defined by total cholesterol >200 or LDL >130

    - Treated or untreated with total cholesterol ≥200 or LDL ≥130

    - Sleep apnea syndrome (confirmed by overnight pO2 studies)

    - Obesity related cardiomyopathy

3. 18-65 years of age inclusive

4. Men or Women. Note: Women of child-bearing potential must have a negative urine pregnancy test at screening and also within 14 days of implant procedure followed by physician-approved contraceptive regimen for the duration of the study period

5. Type 2 diabetes mellitus subjects with:

    - Glycosylated hemoglobin (HbA1c) 7-10% inclusive at screening visit (Undiagnosed subjects that are found to have a HbA1c 7-10% at screening must see their primary physician for diagnosis and medical treatment before continuing in trial);

    - Onset: 12 years or less since initial diagnosis;

    - Currently not using insulin therapy, GLP-1 receptor agonists (e.g., exenatide), for diabetes treatment and have not been on these treatments in the past 6 months;

    - Creatinine within normal reference range;

- No history peripheral neuropathy; autonomic neuropathy; coronary artery disease; or peripheral vascular disease

6. Failure to respond to a supervised diet/exercise programs in which the subject was engaged within the last five years

7. Ability to complete all study visits and procedures

4.2.5 Exclusion Criteria

1. Concurrent chronic pancreatic disease

2. History of Crohn's disease and/or ulcerative colitis, bariatric surgery, fundoplication, gastric resection or major upper-abdominal surgery (acceptable surgeries include cholecystectomy, hysterectomy), pulmonary embolism or blood coagulation disorders

3. Clinically significant hiatal hernias (>5 cm) known from subject's medical record or determined by barium swallow (upper GI x-ray) or upper endoscopy per PI discretion prior to implant.

4. Current cirrhosis, portal hypertension and/or esophageal varices.

5. Intra-operative exclusion: hiatal hernia requiring surgical repair or extensive dissection at esophagogastric junction at time of surgery

6. Treatment with prescription weight-loss drug therapy within the prior three months and the use of prescription drug therapy or the use of over-the-counter weight loss preparations for the duration of the trial

7. Smoking cessation within the prior six months

8. Known genetic cause of obesity (e.g., Prader-Willi Syndrome)

9. Weight loss of more than 10% TBL in the previous 12 months

10. Physician-prescribed pre-operative weight loss program prior to surgery. Note: Study subject may continue any personal eating plan they were on prior to study enrollment.

11. Current type 1 diabetes mellitus

12. Current or recent history (within 12 months) of ongoing bulimia

13. Current alterations in treatment for thyroid disorders (stable treatment regimen for prior three months acceptable)

14. Current alterations in treatment for epilepsy (stable treatment regimen for prior six months acceptable)

15. Current treatment for peptic ulcer disease (previous history acceptable)

16. Chronic treatment (more than 4 weeks of daily use) with narcotic analgesic drug regimens (treatment with non-steroidal anti-inflammatory drugs acceptable)

17. Current alterations in treatment regimens of anti-cholinergic drugs, including tricyclic antidepressants (stable treatment regimen for prior six months acceptable)

18. Current medical condition that, in the opinion of the investigator, would make subject unfit for surgery under general anesthesia or that would be exacerbated by intentional weight loss. Some examples include diagnosis of cancer, recent heart attack, recent stroke, or recent serious trauma.

19. Presence of permanently implanted electrical powered medical device or implanted gastrointestinal device or prosthesis (e.g., pacemakers, implanted defibrillators, neurostimulators etc.)

20. Planned or contemplated use of Magnetic Resonance Imaging (MRI) or oncologic radiation during the course of the trial

21. Psychiatric disorders (including untreated severe depression, schizophrenia, substance abuse, bulimia nervosa, etc.) or limited intellectual functioning which would potentially compromise the participant's ability to fully comprehend and/or cooperate with the study protocol. Psychiatric disorders will be established by a review of subject's medical history. For depression, a BDI score ≥29 was considered to indicate severe depression.

22. Current, active member of an organized weight loss program (e.g., Weight Watchers, TOPS)

23. Current participant in another weight loss study or other clinical trials

24. Have a friend or family member who is currently participating or is planning to participate in this clinical trial

25. Patient reported inability to walk for about 10 minutes without stopping, feeling of pain in chest when doing physical activity, or feeling of pain in chest when not doing physical activity (unless pain in chest known to be related to upper gastrointestinal disorders such as gastroesophageal reflux disease or heartburn

26. Clinically significant cardiac rhythm disorder that requires either medical and/or surgical intervention (e.g., paroxysmal or chronic atrial fibrillation).

4.2.6 Primary Endpoints

4.2.6.1 Primary Efficacy Endpoints

The first co-primary efficacy objective was to demonstrate super-superiority in %EWL with a mean treatment difference between the VBLOC and sham control groups statistically greater than 10 percentage points at 12 months post-randomization. The %EWL using the BMI method, where ideal body weight is the weight corresponding to a BMI of 25 kg/m^2, is calculated as:

*%EWL = (weight lost) / (baseline weight – ideal body weight) * 100%*

The second co-primary efficacy objective was to demonstrate responder rates in the VBLOC arm at 12 months as follows:

- At least 55% of VBLOC subjects achieve at least 20% EWL, and
- At least 45% of VBLOC subjects achieve at least 25% EWL

A secondary endpoint was to demonstrate a difference of at least 10% EWL, as measured by the MetLife method at 12 months post-randomization. This endpoint was to be evaluated only if both primary endpoints were met. As described further in this document, the primary endpoints were not achieved, so efficacy results by the MetLife method will not be discussed further in this document.

4.2.6.2 Primary Safety Endpoint

The primary safety objective was to demonstrate that the 12-month implant/revision procedure, device or therapy-related SAE rate was significantly lower than 15% in the VBLOC group. The 15% performance goal was an upper bound that was based on the adverse event information available on the labels for the FDA-approved LAGB devices. [28,29]

4.2.7 Statistical Methodology

A sample size of 198 subjects with 132 randomized to VBLOC and 66 randomized to the sham control was necessary based upon 85% desired power, type-I error rate of 0.025, a superiority margin of 10% and expected mean weight loss of 25% EWL and 5% EWL for VBLOC and sham control, respectively (SD of mean difference=22%). Assuming a 15% attrition rate before 12 months, 234 subjects were required.

All primary analyses were conducted under the ITT principle and included all randomized subjects. Subjects without a 12-month weight had their value imputed using the LOCF method for the primary analysis per the statistical analysis plan. If a subject was not implanted and had no follow-up visits, 0% EWL was imputed for ITT analyses.

For the co-primary endpoint of the mean difference in %EWL, a one-sided, two-sample t-test at the 0.025 significance level was used to assess whether the VBLOC group had a 10 percentage points or greater difference in %EWL at 12 months post-randomization. The co-primary responder rate endpoints were not statistically based.

A one-sided, one-sample exact binomial test at the 0.025 significance level was used to assess whether the proportion of subjects in the VBLOC group experiencing an implant/revision procedure, device, or therapy-related SAE was less than the 15% performance goal.

Analyses of the co-primary efficacy endpoints were also conducted in the per-protocol population. The per-protocol population was defined as the subjects implanted according to randomization with a 12-month visit that had been initiated within 45 days of implantation and did not have a medical condition that required a discontinuation of therapy for 2 or more months.

4.3 SUBJECT DISPOSITION

Between May and December 2011, 162 and 77 subjects were randomized to VBLOC or sham control, respectively. Six subjects were not implanted after they were randomized. One patient randomized to the sham control group changed their mind immediately before surgery and was not implanted. There were five subjects randomized to VBLOC who were not implanted. Reasons included intra-operative exclusions, failure to implant due to a comorbid condition, or discretion of the implanting physician. These subjects are included in the ITT population.

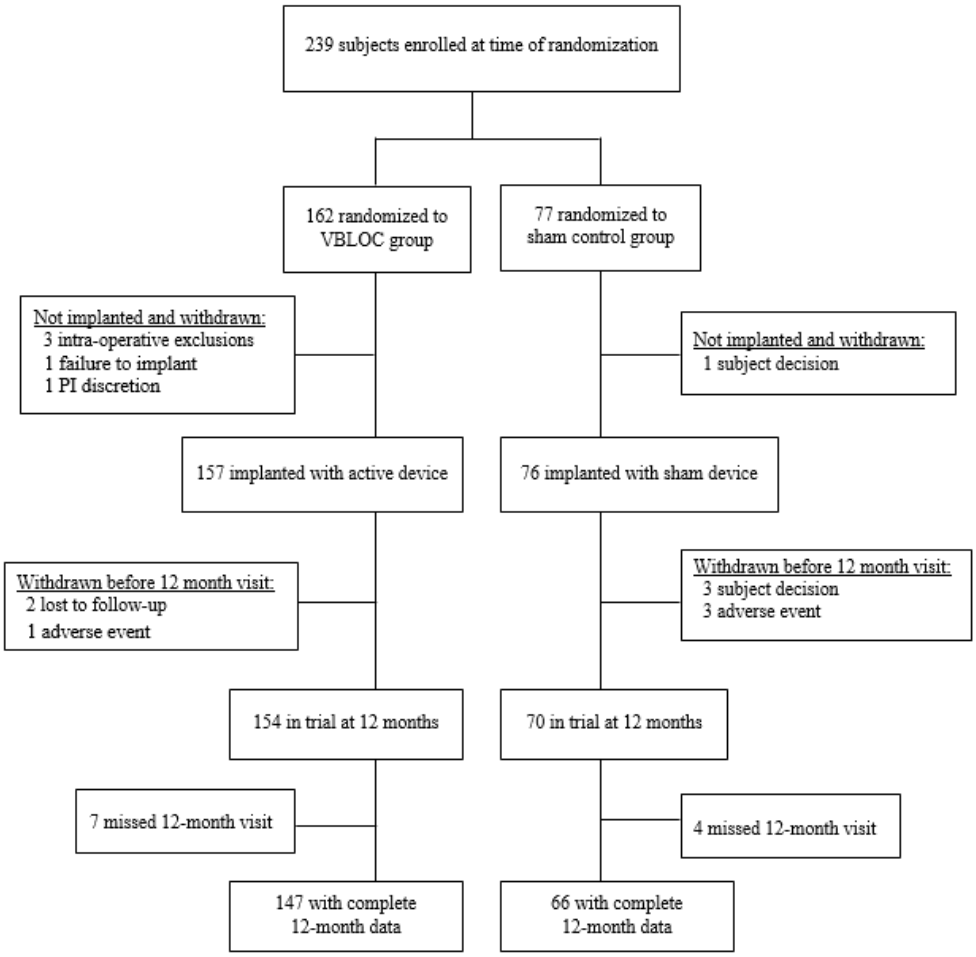
Four (4) subjects (3 sham control, 1 VBLOC) withdrew before 12 months due to adverse events. One VBLOC subject withdrew for pain at the neuroregulator site. One sham control subject withdrew for pain at the neuroregulator site, one due to breast cancer and one due to anxiety. There were no withdrawals due to device malfunction.

Ten subjects were still enrolled in the study but missed the 12-month visit. Of the 162 subjects randomized to VBLOC and 77 to sham control, 147 (90.7%) and 66 (85.7%) had 12-month follow-up data. Subject disposition through is illustrated in Table 4-2 and Figure 4-2 below.

Table 4-2: Subject Disposition through 18-Month Visit

Study Period	VBLOC	Sham Control	Overall
Randomized	**100.0% (162/162)**	**100.0% (77/77)**	**100.0% (239/239)**
Not implanted and withdrawn	3.1% (5/162)	1.3% (1/77)	2.5% (6/239)
Implanted	**96.9% (157/162)**	**98.7% (76/77)**	**97.5% (233/239)**
Implanted and withdrawn before 12-month visit	1.9% (3/162)	7.8% (6/77)	3.8% (9/239)
Total in the trial at 12-month visit	**95.1% (154/162)**	**90.9% (70/77)**	**93.7% (224/239)**
Completed 12-month visit	90.7% (147/162)	85.7% (66/77)	89.1% (213/239)
Did not complete 12-month visit	4.3% (7/162)	5.2% (4/77)	4.6% (11/239)
Total in the trial at 18-month visit	**87.7% (142/162)**	**83.1% (64/77)**	**86.2% (206/239)**
Completed 18-month visit	72.2% (117/162)	54.5% (42/77)	66.5% (159/239)
Did not complete 18-month visit	15.4% (25/162)	28.6% (22/77)	19.7% (47/239)

Figure 4-2: Subject Disposition through 12 Months



At the 18-month visit, 86.2% of randomized subjects were still enrolled in the study. Reasons for withdrawal through 12 months are shown in Table 4-3 and reasons for withdrawal between 12 and 18 months are shown in Table 4-4.

Table 4-3: Reasons for Study Withdrawal through 12 Months

Withdrawal Reason	VBLOC	Sham Control
Failure to implant (cirrhotic liver)	1 (0.6%)	0 (0.0%)
Inclusion/exclusion criteria	3 (1.9%)	0 (0.0%)
PI decision	1 (0.6%)	0 (0.0%)
Adverse event	1 (0.6%)	3 (3.9%)
Lost to follow-up	2 (1.2%)	0 (0.0%)
Subject decision	0 (0.0%)	4 (5.2%)

Table 4-4: Reasons for Study Withdrawal between 12 and 18 Months

Withdrawal Reason	VBLOC	Sham Control
Adverse event	1 (0.6%)	3 (3.9%)
Subject decision	11 (6.8%)	3 (3.9%)

4.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Among the 239 randomized subjects, the average age was 47 years and 85% of subjects were female). The average BMI at implant was 40.9±2.9 kg/m^2. Thirteen subjects (5.4%) were recorded as having diabetes mellitus at screening. The VBLOC and sham control groups were well balanced on demographic and medical history variables of interest (Table 4-5).

Table 4-5: Baseline Demographics and Health Characteristics

Characteristic	VBLOC N=162	Sham Control N=77	P-value
Gender			
Female	141 (87.0%)	62 (80.5%)	0.245
Male	21 (13.0%)	15 (19.5%)	
Age (years) at screening	47.1 ± 10.3	46.6 ± 9.4	0.693*
Race			
Caucasian	149 (92.0%)	73 (94.8%)	0.592
African American	8 (4.9%)	3 (3.9%)	1.000
Native American	2 (1.2%)	1 (1.3%)	1.000
Asian	1 (0.6%)	1 (1.3%)	0.541
Hawaiian/Pacific Islander	1 (0.6%)	0 (0.0%)	1.000
Height (m) at screening	1.7 ± 0.1	1.7 ± 0.1	0.112*
BMI at implant (kg/m^2)	40.9 ± 2.8	40.9 ± 3.1	0.969*
Weight at implant (kg)	112.6 ± 13.4	115.5 ± 14.3	0.117
Excess weight (kg) at implant	43.7 ± 8.7	44.9 ± 9.5	0.371
Waist circumference (cm) at screening	121.1 ± 11.8	123.0 ± 11.3	0.236
Type 2 diabetes mellitus	9 (5.6%)	6 (7.8%)	0.571
Hypertension	63 (38.9%)	32 (41.6%)	0.920
Dyslipidemia	91 (56.2%)	46 (59.7%)	0.884
Obstructive sleep apnea	33 (20.4%)	23 (29.9%)	0.267

Note: Data are presented as mean ± SD for continuous variables. Data are presented as n (%) for categorical variables. P-values for continuous variables were calculated using a Student's t-test (no asterisk) or a Wilcoxon rank sum test (*) if the variable was not normally distributed based on the Shapiro-Wilk normality test. Categorical variables were compared using Fisher's exact test.

4.5 THERAPY DELIVERY

Since therapy cannot be delivered during recharging, the device was programmed to deliver 13 hours of therapy per day to achieve a minimum of 12 hours actual therapy delivery per day. The neuroregulator in the sham control group dissipated energy but did not have leads attached to vagus nerve. Device use was recorded for the sham group in order to assess compliance with recharging between groups.

Through 12 months of follow-up, the average hours per day of device use was 12.2 in the VBLOC group and 12.0 in the sham control group (Table 4-6). The mean amplitude from implant to 12 months was 5.7 in the VBLOC group and 6.1 in the sham control group. Devices were to be programmed to deliver 6 mA or the maximum tolerated amplitude, so the majority of patients achieved this level (Table 4-7).

Table 4-6: Hours of Use through 12 Months of Follow-up

Device use measure	VBLOC	Sham Control
Hours of device use per day	12.2 ± 1.3 (157)	12.0 ± 1.5 (76)
Percentage of days followed with any device use	96% ± 8.5 (157)	95% ± 11.5 (76)
Percentage of days followed with ≥12 hours of device use	88% ± 11 (157)	87% ± 13 (76)

Note: Data are Mean ± SD (N). Table does not include those subjects who were not implanted.

Table 4-7: Mean Amplitude from Implant to Month 12

Group	N	Mean	SD	Median	Min	Max
VBLOC	157	5.7	0.8	5.9	2.0	6.8
Sham Control	76	6.1	0.5	6.1	3.0	6.7

Trends in device use had not changed at 18 months. The average hours of use was 12.1 ± 1.6 hours in the VBLOC group and 11.9 ± 1.6 hours in the sham control. The mean amplitude through 18 months was 5.9 ± 1.0 in the VBLOC group and 6.3 ± 0.6 in the sham control group.

4.6 EFFICACY

4.6.1 Primary Efficacy Endpoints – ITT Population

At 12 months in the ITT-LOCF population, the mean %EWL in the VBLOC group was 24.4% compared to 15.9% in the sham control group (Table 4-8). The treatment difference between groups was 8.5 percentage points (95% CI, 3.1 to 13.9), which demonstrated superiority of VBLOC over sham but did not meet the co-primary objective of achieving a 10-point superiority margin for %EWL.

Table 4-8: Co-Primary Efficacy Endpoint (Mean Difference in %EWL) in ITT-LOCF Population

%EWL	VBLOC	Sham Control	Difference
N	162	77	
Mean ± SD	24.4 ± 23.6	15.9 ± 17.7	8.5 ± 21.9
[95% CI]	[20.8, 28.1]	[11.9, 19.9]	[3.1, 13.9]
Super-Superiority P-value			0.708

Overall in the ITT-LOCF population, 52.5% of subjects in the VBLOC group achieved at least 20% EWL and 38.3% of subjects achieved at least 25% EWL. Neither responder rate met the pre-specified thresholds, however 55% of VBLOC subjects achieved at least 18% EWL, and 45% of subjects achieved at least 23% EWL.

4.6.2 Primary Efficacy Endpoints – Per-Protocol Population

In the per-protocol population, the mean %EWL was 26.3% and 17.3% for the VBLOC and sham control groups, respectively (Table 4-9). The mean difference between groups was 8.9 percentage points (95% CI, 3.0 to 14.8).

Table 4-9: Co-Primary Efficacy Endpoint (Mean Difference in %EWL) in Per-Protocol Population

%EWL	VBLOC	Sham Control	Difference
N	146	65	
Mean ± SD	26.3 ± 23.8	17.3 ± 18.1	8.9 ± 22.2
[95% CI]	[22.4, 30.2]	[12.9, 21.8]	[3.0, 14.8]
Super-Superiority P-value			0.64

In the per-protocol population, 56.8% of subjects in the VBLOC group achieved at least 20% EWL and 41.8% achieved at least 25% EWL. The proportion of VBLOC subjects achieving at least 20% EWL met the performance goal; however, the proportion for the 25% EWL threshold did not.

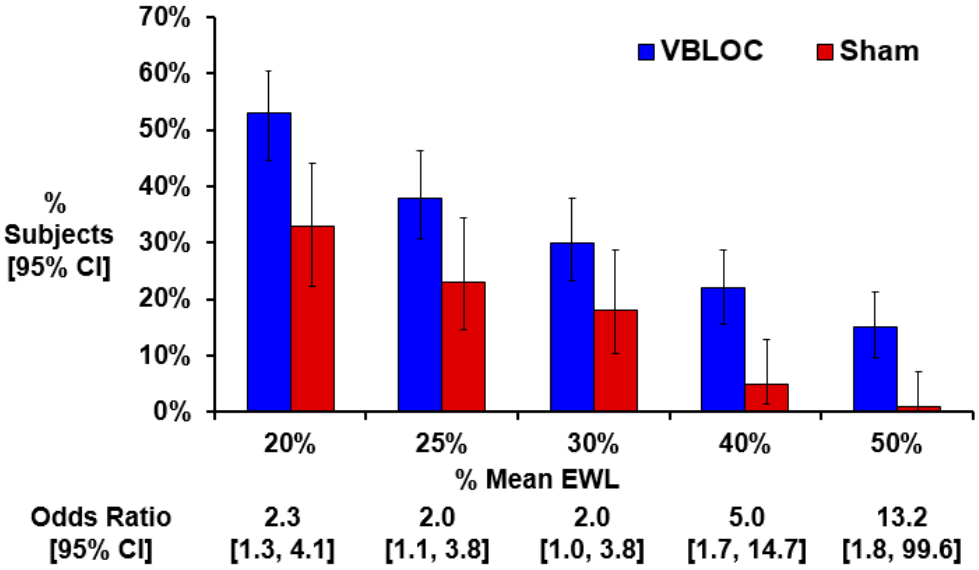
4.6.3 Additional Responder Rate Analyses

Further exploratory analyses of responder rates were conducted to compare the percentage of subjects in each group who achieved levels of response between 20% and 50% EWL. As shown in Table 4-10, significantly higher proportions of VBLOC subjects achieved the %EWL thresholds compared to sham control subjects. The VBLOC group had significantly higher odds of achieving higher %EWL thresholds over sham control at every threshold from 20% through 50%. Further, the odds of a VBLOC subject achieving weight loss thresholds over a sham control subject increased as weight loss thresholds became more difficult to attain (Figure 4-3).

Table 4-10: %EWL Responder Analysis in ITT-LOCF Population at 12 Months

%EWL Achieved	VBLOC	Sham Control	OR [95% CI]
20% EWL	85 (52.5%)	25 (32.5%)	2.3 [1.3, 4.1]
25% EWL	62 (38.3%)	18 (23.4%)	2.0 [1.1, 3.8]
30% EWL	49 (30.2%)	14 (18.2%)	2.0 [1.0, 3.8]
40% EWL	35 (21.6%)	4 (5.2%)	5.0 [1.7, 14.7]
50% EWL	24 (14.8%)	1 (1.3%)	13.2 [1.8, 99.6]

Figure 4-3: %EWL Responder Analysis in ITT-LOCF Population at 12 Months



A similar trend is observed with %TBL as was observed with %EWL (Table 4-11). As %TBL thresholds become higher and more difficult to attain, the odds of success increase considerably for the VBLOC group compared to the sham control group.

Table 4-11: %TBL Responder Analysis in ITT-LOCF Population at 12 Months

%TBL Achieved	VBLOC	Sham Control	OR [95% CI]
5.0% TBL	103 (63.6%)	41 (53.2%)	1.5 [0.9, 2.7]
7.5% TBL	84 (51.9%)	27 (35.1%)	2.0 [1.1, 3.5]
10.0% TBL	58 (35.8%)	14 (18.2%)	2.5 [1.3, 4.9]
15.0% TBL	33 (20.4%)	4 (5.2%)	4.7 [1.6, 13.7]
20.0% TBL	19 (11.7%)	1 (1.3%)	10.1 [1.3, 76.9]

4.6.4 Efficacy through 18 Months

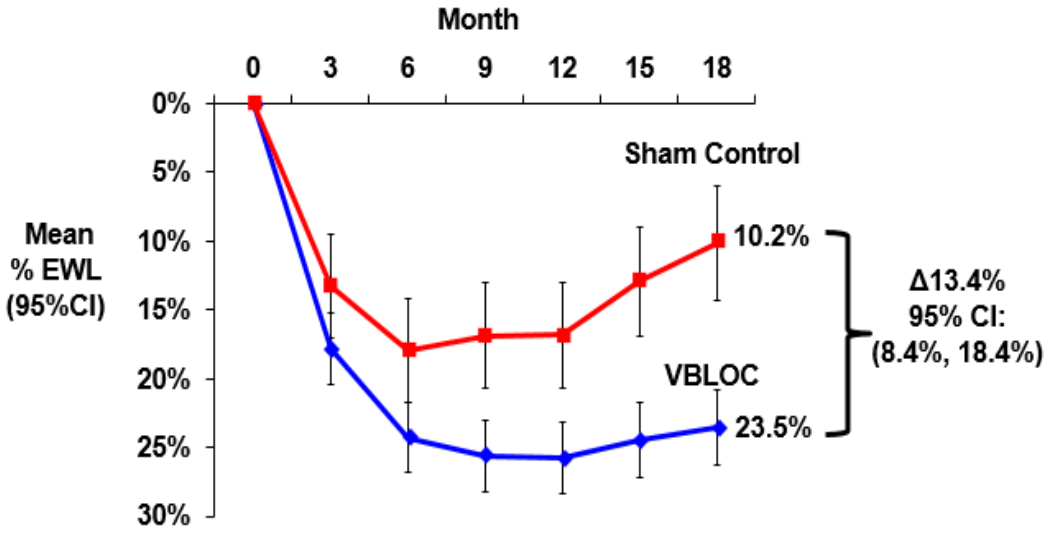
Efficacy through 18 months was assessed using a mixed-effects regression model using all available follow-up data in the ITT sample, the ITT-LOCF methodology, as well as without imputation. Eighteen-month data were recorded for 159 subjects (117 VBLOC and 42 sham control). Since the trial remained blinded until all subjects had completed the 12-month visit, most subjects remained blinded until the 16-month visit. At 15 months, 84% of VBLOC subjects and 90% of sham control subjects remained blinded. At 18 months, 27% of VBLOC subjects and 25% of sham control subjects remained blinded.

Results from the mixed-effects model in the ITT sample suggest that weight loss with VBLOC therapy was durable, with an estimated mean 25.8% EWL at 12 months, 24.4% at 15 months, and 23.5% EWL at 18 months. The sham control group regained a significant amount of weight following the 12-month visit, with an estimated mean %EWL of 16.9% at 12 months, 12.9% at 15 months, and 10.1% at 18 months (Table 4-12). The treatment difference increased from 8.9 percentage points (95% CI: 4.3 to 13.5) at 12 months to 13.4 percentage points (95% CI: 8.4 to 18.4) at 18 months. This increase in relative efficacy as a result of the sham control group gaining weight cannot be largely attributed to unblinding since most subjects remained blinded until the 16-month visit.

Table 4-12: ITT-Mixed-Effects Model Estimates for %EWL at 12, 15 and 18 Months

Visit Month	VBLOC Mean [95% CI]	Sham Control Mean [95% CI]	Difference Mean [95% CI]
12 months	25.8% [23.2, 28.3]	16.9% [13.1, 20.7]	8.9 [4.3, 13.5]
15 months	24.4% [21.7, 27.1]	12.9% [9.0, 16.9]	11.5 [6.7, 16.3]
18 months	23.5% [20.8, 26.2]	10.1% [5.9, 14.3]	13.4 [8.4, 18.4]

Figure 4-4: ITT-Mixed-Effects Model Estimates of %EWL through 18 Months



In the ITT-LOCF population at 18 months, the VBLOC group had a mean 21.1% EWL and the sham control group had a mean 11.0% EWL (Table 4-13). The mean difference between groups was 10.0 percentage points (95% CI: 4.6 to 15.4).

Table 4-13: Mean %EWL at 18 Months in ITT-LOCF Population

%EWL	VBLOC	Sham Control	Difference
N	162	77	
Mean ± SD	21.1 ± 23.8	11.0 ± 17.4	10.0 ± 21.9
[95% CI]	[17.4, 24.7]	[7.1, 15.0]	[4.6, 15.4]
Superiority P-value			<0.001

In the ITT-LOCF population at 18 months, 46% in the VBLOC group had achieved 20% EWL and 35% had achieved 25% EWL (Table 4-14).

Table 4-14: %EWL Responder Rates at 18 Months in ITT-LOCF Population

%EWL achieved	VBLOC	Sham Control	OR [95% CI]
20% EWL	75 (46.3%)	20 (26.0%)	2.5 [1.4, 4.5]
25% EWL	56 (34.6%)	11 (14.3%)	3.2 [1.5, 6.5]
30% EWL	44 (27.2%)	5 (6.5%)	5.4 [2.0, 14.2]
40% EWL	29 (17.9%)	3 (3.9%)	5.4 [1.6, 18.3]
50% EWL	23 (14.2%)	1 (1.3%)	12.6 [1.7, 94.9]

As shown in Table 4-15, the mean %EWL as observed among subjects attending the 18-month visit was 25.2% in the VBLOC group and 11.7% in the sham control group.

Table 4-15: Mean %EWL at 18 Months among Subjects Completing 18-Month Visit

%EWL	VBLOC	Sham Control	Difference
N	117	42	
Mean ± SD	25.2 ± 25.3	11.7 ± 20.3	13.5 ± 24.1
[95% CI]	[20.6, 29.8]	[5.4, 18.0]	[5.7, 21.3]
Superiority P-value			<0.001

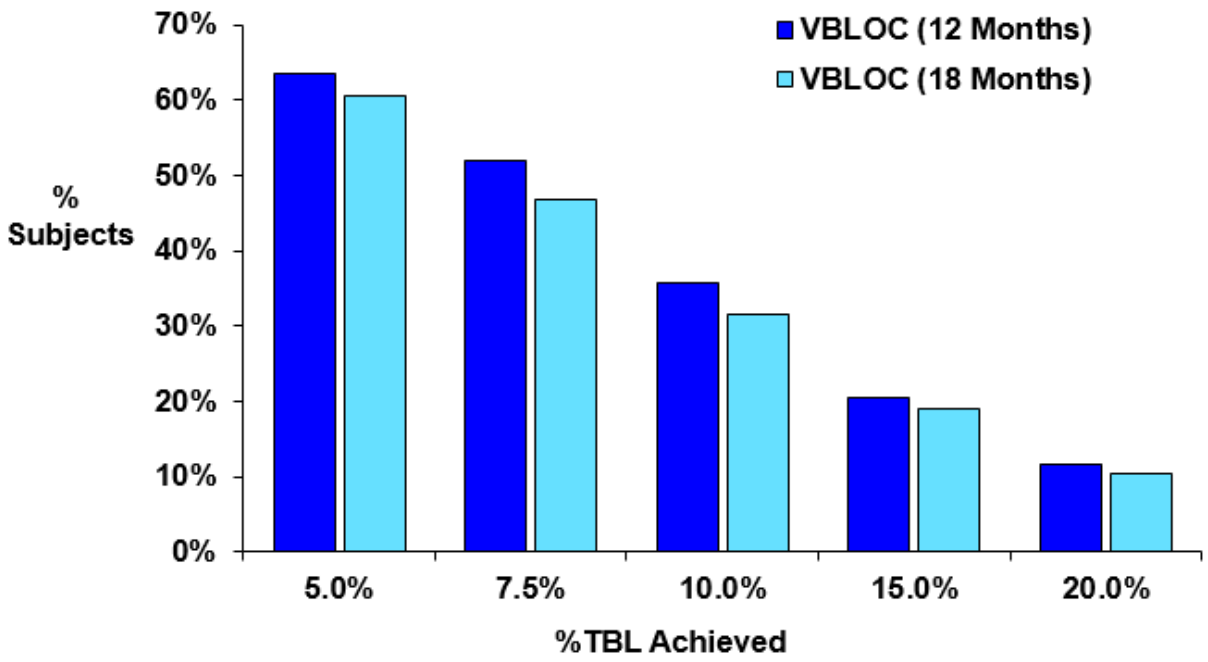
As shown in Table 4-16, among subjects completing the 18-month visit, 54% of subjects in the VBLOC arm achieved at least 20% EWL and 41% of subjects achieved at least 25% EWL.

Table 4-16: %EWL Responder Rates at 18 Months among Subjects Completing 18-Month Visit

%EWL achieved	VBLOC N=117	Sham Control N=42	OR [95% CI]
20% EWL	63 (53.8%)	11 (26.2%)	3.3 [1.5, 7.2]
25% EWL	48 (41.0%)	7 (16.7%)	3.5 [1.4, 8.5]
30% EWL	38 (32.5%)	4 (9.5%)	3.6 [1.5, 13.7]
.40% EWL	28 (23.9%)	2 (4.8%)	6.3 [1.4, 27.7]
50% EWL	23 (19.7%)	1 (2.4%)	10.0 [1.3, 76.8]

With regard to %TBL, ITT-LOCF responder rate analysis of the %TBL thresholds achieved by the VBLOC group showed durability of effect from 12 to 18 months (Figure 4-5).

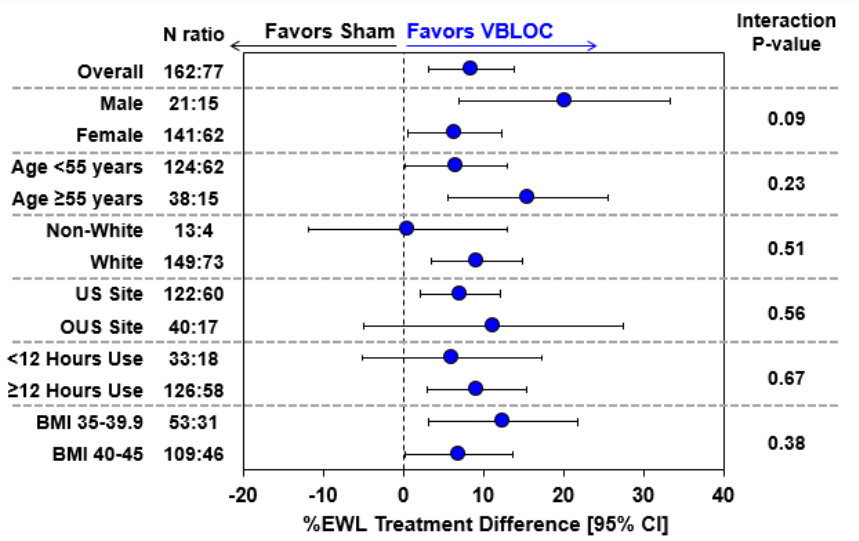
Figure 4-5: %TBL ITT-LOCF Responder Analysis in VBLOC Group at 12 and 18 Months



4.6.5 Subgroup Analysis

Figure 4-6 shows the mean treatment difference in %EWL between VBLOC and sham control by pre-defined subgroups: gender, age, race, BMI at implant, geography, and hours of use. There were no significant interactions between treatment and subgroup in mean %EWL.

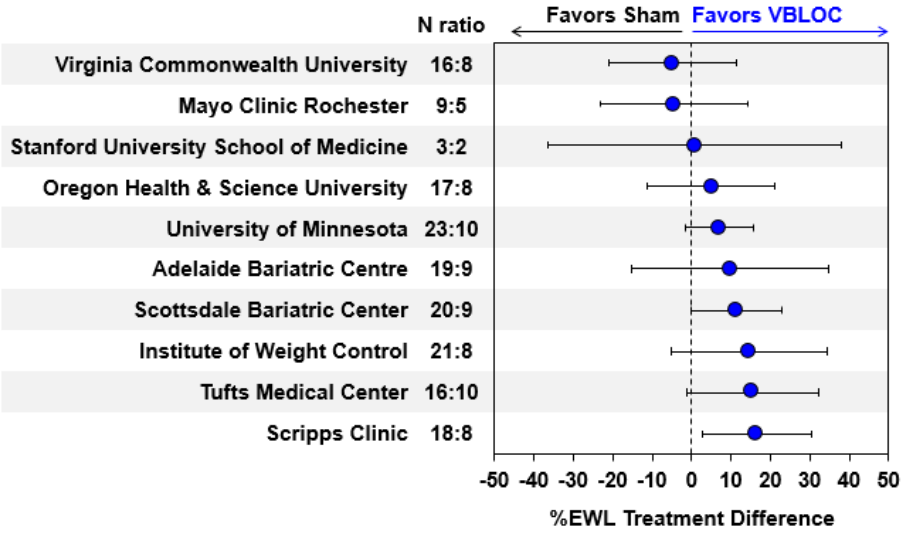
Figure 4-6: Treatment Effect by Subgroups in ITT-LOCF Population at 12 Months



4.6.6 Poolability Analysis

The poolability of the co-primary efficacy endpoint (mean %EWL treatment difference) across centers was assessed with the treatment by site interaction using a linear regression model. The overall significance of the interaction was 0.72, suggesting that there was no significant evidence that the treatment effect was significantly different by site.

Figure 4-7: Treatment Effect by Site in ITT-LOCF Population at 12 Months



4.6.7 Improvement in Metabolic, Cardiovascular and Anthropometric Parameters

Changes in metabolic, cardiovascular, and waist circumference were observed in both groups, commensurate with weight loss (Table 4-17). Many of the improvements from baseline were statistically significant in both groups (with no adjustment for multiple comparisons) and are of a similar magnitude to those observed for other studies demonstrating the clinical benefits of weight loss for obese individuals. All differences between groups were not significant with the exception of reduction in waist circumference, which was significantly greater in the VBLOC group.

Table 4-17: Change in Metabolic, Cardiovascular and Anthropometric Risk Factors at 12 Months

Risk Factor	VBLOC	Sham Control	Difference
Metabolic			
Total Cholesterol (mg/dL)	-9 [-14, -4]	-10 [-17, -3]	1 [-8, 10]
LDL Cholesterol (mg/dL)	-5 [-10, -1]	-4 [-10, 2]	-1 [-8, 6]
HDL Cholesterol (mg/dL)	1 [-1, 3]	0 [-3, 2]	1 [-2, 4]
Triglycerides (mg/dL)	-21 [-31, -12]	-33 [-48, -18]	12 [-6, 29]
Fasting Plasma Glucose (mg/dL)	-1.5 [-4.1, 1.0]	-0.7 [-3.5, 2.2]	-0.9 [-4.6, 2.9]
Hemoglobin A1c (%)	-0.3 [-0.4, -0.3]	-0.3 [-0.4, -0.2]	0.0 [-0.1, 0.1]
Cardiovascular			
Systolic Blood Pressure (mmHg)	-6 [-8, -3]	-4 [-7, -1]	-2 [-6, 3]
Diastolic Blood Pressure (mmHg)	-3 [-4, -1]	-4 [-7, -2]	2 [-1, 4]
Heart Rate (bpm)	-4 [-5, -2]	-4 [-6, -1]	0 [-3, 3]
Anthropometric			
Waist Circumference (cm)	-10 [-12, -9]	-8 [-10, -6]	-2 [-5, 0]

Note: Data are mean change [95% CI].

In addition to assessing mean changes in HbA1C and fasting plasma glucose (FPG), an exploratory analysis of the impact of weight loss in the VBLOC group on risk for diabetes was conducted. There were 110 VBLOC patients with both screening and 12-month data who were not on a medication for diabetes, hyperglycemia, or other endocrine disorder at any time during the first 12 months of the study.

For this analysis, we considered a normal status to require both fasting plasma glucose (FPG) <100 mg/dL and HbA1c <5.7%. We defined pre-diabetes as FPG ≥100 mg/dL or HbA1c ≥5.7%. At screening, 55 patients had normal values and 55 patients had pre-diabetic values in the VBLOC group. As shown in Table 4-18, at 12 months, 58% of the patients who had levels in the pre-diabetes range at baseline improved to a normal status at 12 months.

Interestingly, this result is remarkably similar to results from the DPP study, which found that 7% TBL resulted in a 58% reduction in risk for the development of type-II diabetes in insulin resistant patients.[4,5]

Table 4-18: Change in Pre-Diabetes Status at 12 Months in VBLOC Group

Screening Status	Month 12 Status	
	Normal	Pre-Diabetic
Normal (n=55)	48 (87.3%)	7 (12.7%)
Pre-Diabetic (n=55)	32 (58.2%)	10 (41.8%)

4.6.8 Three Factor Eating Questionnaire (TFEQ)

The Three Factor Eating Questionnaire (TFEQ) is a validated, self-report questionnaire that is used to measure the psychological constructs of eating on three subscales: cognitive restraint, disinhibition, and hunger.[30] Of these, the hunger factor is of most interest, since decreasing hunger and earlier satiety are consistent with the mechanism of action of VBLOC therapy. The results through 12 months show that scores on each factor improved. At 18 months, similar to weight loss results, the VBLOC group had maintained its improvements while the sham control had lost some of the improvements reported through 12 months.

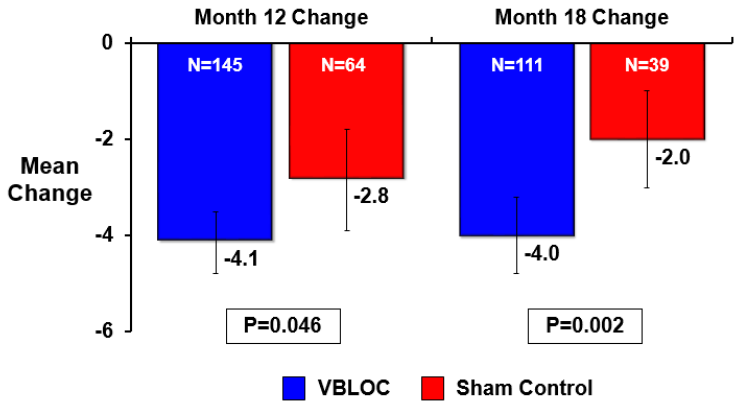
The hunger factor on the TFEQ has a range of 0 to 14, with higher scores indicating greater sensations of hunger. At screening, both groups had a score of approximately 8. At 12 months, significant improvements in both groups were observed, but greater reductions were observed in the VBLOC group (Table 4-19, Figure 4-8). At 18 months, the VBLOC group had maintained its improvement in hunger, but improvements diminished in the sham group.

Table 4-19: TFEQ Hunger Factor Scores through 18 Months

Study Visit	VBLOC	Sham Control	Difference
Screening	8.0 ± 3.3 (160) [7.4, 8.5]	7.9 ± 3.8 (77) [7.0, 8.7]	0.1 ± 3.4 [-0.9, 1.1]
12 month change	-4.1 ± 3.9 (145) [-4.8, -3.5]	-2.8 ± 4.3 (64) [-3.9, -1.8]	-1.3 ± 4.0 [-2.5, 0.0]
18 month change	-4.0 ± 4.1 (111) [-4.8, -3.2]	-2.0 ± 3.2 (39) [-3.0, -1.0]	-2.0 ± 3.9 [-3.3, -0.7]

Note: Data are mean ± SD (N) [95% CI].

Figure 4-8: Change in TFEQ Hunger Factor



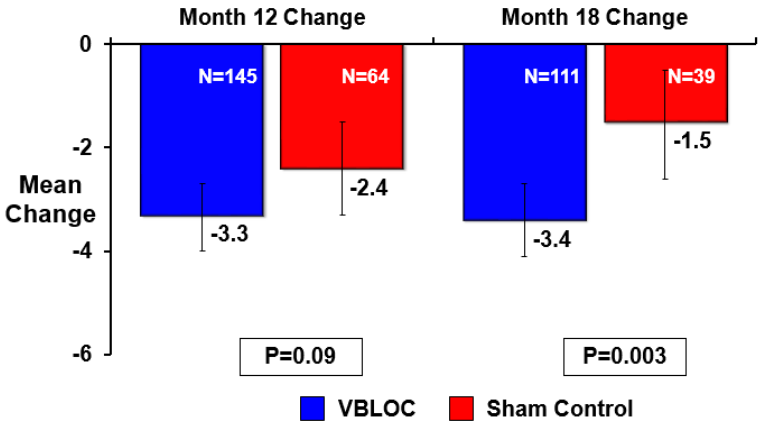
The disinhibition factor on the TFEQ has a range of 0 to 16, with higher scores indicating greater loss of control over food intake. At screening, both groups had a score of approximately 10. Similar to the hunger factor, at 12 months, the improvements were greater in the VBLOC group than the sham control group, and these improvements were maintained in the VBLOC group through 18 months while the improvements in the sham group were diminished at 18 months (Table 4-20, Figure 4-9).

Table 4-20: TFEQ Disinhibition Factor Scores through 18 Months

Study Visit	VBLOC	Sham Control	Difference
Screening	10.3 ± 3.3 (160) [9.8, 10.9]	10.1 ± 3.3 (77) [9.3, 10.8]	0.3 ± 3.3 [-0.6, 1.2]
12 month change	-3.3 ± 3.7 (145) [-4.0, -2.7]	-2.4 ± 3.7 (64) [-3.3, -1.5]	-1.0 ± 3.7 [-2.1, 0.1]
18 month change	-3.4 ± 3.8 (111) [-4.1, -2.7]	-1.5 ± 3.2 (39) [-2.6, -0.5]	-1.9 ± 3.6 [-3.2, -0.6]

Note: Data are mean ± SD (N) [95% CI].

Figure 4-9: Change in TFEQ Disinhibition Factor

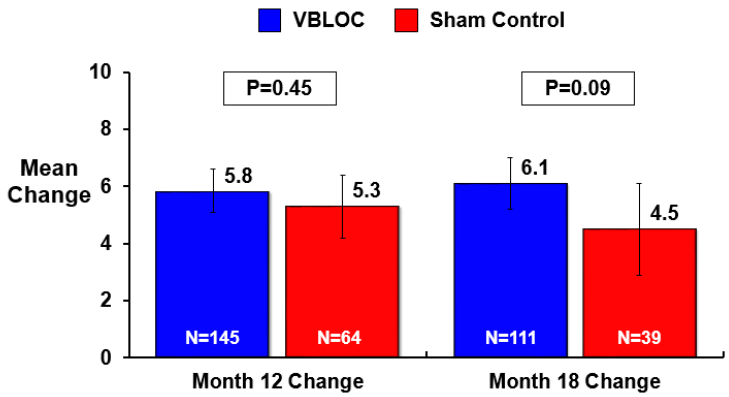


The cognitive restraint factor on the TFEQ has a range of 0 to 21, with higher scores indicating greater intentional efforts to limit food intake. At screening, both groups had a score of approximately 9.5. Significant improvements from baseline in both groups were observed at 12 and 18 months, but no significant difference was observed between groups at 12 or 18 months (Table 4-21, Figure 4-10).

Table 4-21: TFEQ Cognitive Restraint Factor Scores through 18 Months

Study Visit	VBLOC	Sham Control	Difference
Screening	9.5 ± 4.4 (160) [8.8, 10.2]	9.2 ± 4.2 (77) [8.3, 10.2]	0.3 ± 4.3 [-0.9, 1.4]
12 month change	5.8 ± 4.7 (145) [5.1, 6.6]	5.3 ± 4.5 (64) [4.2, 6.4]	0.5 ± 4.6 [-0.8, 1.9]
18 month change	6.1 ± 4.6 (111) [5.2, 7.0]	4.5 ± 5.0 (39) [2.9, 6.1]	1.6 ± 4.7 [-0.3, 3.4]

Figure 4-10: Change in TFEQ Cognitive Restrain Factor



4.6.9 Impact of Weight on Quality of Life-Lite (IWQoL-Lite) Questionnaire

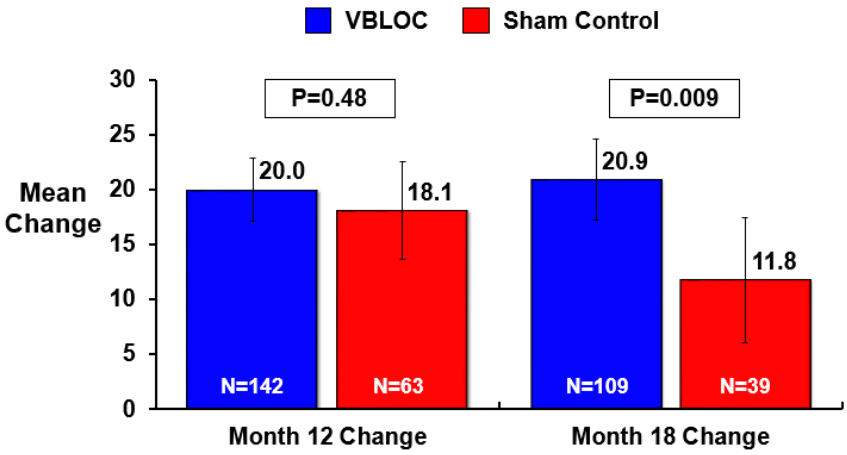
IWQoL-Lite is a validated quality of life instrument that includes 31 questions that measure 5 domains: physical function, self-esteem, sexual life, public distress and work.[31] Scores range from 0 to 100, with higher scores indicating greater quality of life. At screening, both groups had scores of about 55. At 12 months, both groups had significant improvements in quality of life, about 20 points on the 100-point scale. At 18 months, the VBLOC group had maintained the observed improvements, while the improvements were diminished in the sham control group (Table 4-22, Figure 4-11).

Table 4-22: IWQoL-Lite Scores through 18 Months

Study Visit	VBLOC	Sham Control	Difference
Screening	57.0 ± 16.6 (157) [54.4, 59.6]	54.1 ± 18.4 (77) [49.9, 58.3]	2.9 ± 17.2 [-2.0, 7.8]
12 month change	20.0 ± 17.5 (142) [17.1, 22.9]	18.1 ± 17.7 (63) [13.6, 22.6]	1.9 ± 17.6 [-3.4, 7.2]
18 month change	20.9 ± 19.7 (109) [17.2, 24.6]	11.8 ± 17.5 (39) [6.1, 17.4]	9.1 ± 19.2 [2.4, 15.8]

Note: Data are mean ± SD (N) [95% CI]

Figure 4-11: Change in IWQoL-Lite Scores



4.6.10 Sham Effect

As previously described, the assumptions of the mean %EWL in the VBLOC group (assumed 25%; observed 24.4%) proved to be approximately correct, however the assumption regarding %EWL in the sham control group was underestimated considerably (assumed 5%, observed 15.9%). The level of weight loss observed in the sham control group was approximately four times greater than what has been observed for placebo controls in obesity drug trials. Possible reasons for the sham effect observed in the ReCharge Study are discussed below.

Patient Population

Obese individuals undergo surgery with the expectation of receiving a significant benefit and may consider the surgical intervention to be their last chance to achieve meaningful weight loss. These patients are only eligible for bariatric surgery after repeated attempts and failures to lose weight through less invasive measures, such as diet programs, exercise regimens, and pharmacotherapy over a considerable period of time. Most patients who undergo bariatric surgery are highly motivated to change their behavior to achieve their weight loss goals.

It is reasonable to conclude that these expectations encouraged adherence to study protocols and suggested lifestyle changes that impacted the weight loss that was observed in the sham group. Jonas[32] discusses the impact of the "inner environment" on clinical response and notes that "expectation – the belief and anticipation of improvement and hope that a desired goal can be achieved – can have a profound impact on healing and response."

Note that this level of patient motivation is different from the improvements that are typically observed for subjects in clinical trials, since the motivation that stems from a patient's decision to undergo bariatric surgery would be present regardless of whether a patient is enrolled in a clinical trial. Therefore, this expectation effect is present in the real world and would be present for patients who elect to receive the Maestro device in a commercial setting.

Sham Surgery

Each sham control patient underwent a surgery under general anesthesia to place the sham neuroregulator and the skin incisions to mimic the trocar placement. The phenomenon of sham surgical effects exceeding those expected of a placebo pill has been observed in other clinical trials including the few randomized controlled trials that have compared surgical intervention to sham surgery for such diverse conditions as angina pectoris,[33] asthma,[34] osteoarthritis of the knee,[35] and Parkinson's disease.[36]

Table 4-23 below compares the sham responses observed in recent clinical trials of other medical devices. It should be noted that all of these medical devices have been approved by the FDA and have proven to be useful treatments.

Table 4-23: Summary of Medical Device Trials Incorporating Sham Controls

Intervention	Sham control	Primary Endpoint Variable assessed	Percent of sham response relative to active arm (%)
Bronchial thermoplasty for Treatment of Severe Asthma (1)	Sham bronchoscopy	Mean change and responder analysis of Asthma Quality of Life Score	86% (mean difference) 81% (responder rate)
Intradiscal electrothermal therapy for Discogenic Low Back Pain (2)	Needle inserted onto disc with no therapy	Mean changes in visual analogue scale (VAS) for pain, SF-36 scales, and Oswestry Disability Scale	46% (VAS) 53% (SF-36 Bodily Pain) 73% (SF-36 Physical Functioning) 36% (Oswestry Disability Scale)
Percutaneous tibial nerve stimulation for overactive bladder syndrome (3)	"Inserted" sham needle that caused sensation of slight needle prick	Changes in urinary frequency, voided volume, subjective response rate, symptom severity score, health-related QoL score	63% (urinary frequency episodes) 43% (nighttime voids) 52% (voided urinary volume) 38% (subjective response rate) 80% (symptom severity score) 60% (health-related QoL score)
Extracorporeal shock wave therapy calcifying tendonitis (4)	No coupling gel used to prevent shock wave transmission	Mean Change in Constant and Murley scale, and responder rate	44% (CMS mean, low energy) 21% (CMS mean, high energy) 41% (CMS responder, low energy) 19% (CMS responder, high energy)

Intervention	Sham control	Primary Endpoint Variable assessed	Percent of sham response relative to active arm (%)
Deep brain stimulation for Epilepsy (5)	Electrodes implanted in the cranium at the seizure focus with no stimulation applied	% change in seizure frequency	45%

The range of the relative response of the sham compared to the active arms of these trials is variable, but the sham response is typically between 40% and 70% that of the active treatment. Taking the ReCharge Study ITT-LOCF results, the relative response would be 65% for the mean effect (15.9% EWL vs. 24.4% EWL) and 62% for the 20% EWL responder effect (32.5% vs. 52.5%). In the context of sham-controlled medical device trials, the relative response of the sham in the ReCharge Study is consistent with that observed in previous studies of FDA-approved medical devices in other treatment areas.

Device Interaction

Both sham and VBLOC subjects in the ReCharge study were required to interact daily with their device. Subjects were instructed to check the battery level using the Mobile Charger attached to the transmit coil positioned over the neuroregulator every day, and to charge the battery at least twice per week, which typically takes 30-90 minutes to complete.

The scientific literature is replete with examples of how enhanced self-monitoring of weight loss goals results in greater weight loss outcomes.[37] Since sham subjects, as well as VBLOC subjects, incorporated the schedule of checking their battery and recharging consistently into their lives, they received the benefit of consistent self-monitoring. This daily reminder of their weight loss goals likely had a positive impact on lifestyle habits. This type of daily interaction with the device would be required in a commercial environment, so the benefits in weight loss achieved would be present for all subjects receiving VBLOC therapy.

Follow-Up Visits and Weight Management Counseling

The ReCharge Study incorporated 17 follow-up visits for both VBLOC and sham control subjects in the first 12 months, which included weight management sessions. These visits included counseling on caloric intake, healthy food choices and the importance of exercise. It is well known in the obesity literature that follow-up visit frequency can have an impact on the weight loss observed.[38] Both VBLOC and sham control subjects had high rates of attendance for follow-up visits and weight management sessions. However, it is important to note that these weight management sessions were not “intensive” and they did not incorporate interventions such as controlled-portion meals, very low calorie diets or pharmacotherapy. In this regard, the weight management program in ReCharge is typical of programs currently being delivered at bariatric centers of excellence.

Summary of Sham Effect

Taken together, the larger-than-expected sham response in the ReCharge study was likely due to a combination of factors including the unique characteristics of the bariatric surgery patient population as well effects of sham surgery, frequent interaction with a sham device, and follow-up. Patients who choose to be treated with the Maestro Rechargeable System will receive all the clinical benefits, including those provided by the surgical placement, patient interaction and self-monitoring with the device, VBLOC therapy, as well as follow-up with their physician. Therefore, in the appraisal of the benefit-risk equation for the device, it is appropriate to focus primarily on the magnitude of the effect in the VBLOC group since this is reflective of the real-world that patients will receive, particularly in light of demonstrating both superior weight loss over sham and the fact that weight loss with a sham intervention is not sustained.

4.7 SAFETY

4.7.1 Summary of Safety

- The primary safety endpoint (the procedure, device or therapy-related SAE rate through 12 months) was met with a related SAE rate of 3.7% (95% CI, 1.4% to 7.9%) in the ITT population, significantly lower than the 15% performance goal ($p<0.0001$).

- Through 12 months, 13.0% of VBLOC subjects and 5.2% of sham control subjects had an SAE regardless of relatedness to device, procedure, or therapy. Of the 26 SAEs reported among 21 subjects in the VBLOC group, 6 were adjudicated as implant/revision procedure, device, or therapy-related and 9 were adjudicated as related to the general surgical procedure.

- The majority of the AEs observed in the ReCharge Study were non-serious and unrelated to the device, procedure, or therapy. At 12 months, 98% of AEs related to treatment were mild to moderate in severity and most resolved with medical therapy or no intervention.

- The most common related AEs reported were pain and GI symptoms, including heartburn, dysphagia, belching and nausea. There is no evidence of any damage to the vagal nerve from VBLOC therapy.

- Eight (8) subjects (4.9%) in the VBLOC group had 9 surgical revisions performed through 12 months: 5 for adverse events, 3 for device malfunction, and 1 subject for other reasons.

- Through 12 months, there were 13 surgical explants of the device (8 in control group and 5 in VBLOC group). All explanted subjects had a hospital stay of one day or less with the exception of one subject (313-329-RC) who had a mastectomy at the time of explant.

- The related SAE rate through 18 months was 4.3% (95% CI: 1.8% to 8.7%). There was one additional related SAE (gastric perforation) that occurred during explantation of the device for subject decision.

- The overall safety profile through 18 months remains similar to that reported at 12 months. The most common AEs related to the device, procedure or therapy, continued to be pain-related, heartburn/dysphagia, procedure-related nausea, eructation/belching, and dysphagia.

Overall, the incidence of any AE was similar between groups (Table 4-24). The relatedness of non-serious AEs and the severity of AEs were assessed by the investigator. Investigators categorized the severity of AEs as mild, moderate, or severe (Table 4-25).

Table 4-24: Summary of AEs through 12 Months

AE Type	VBLOC		Sham Control		Difference [95% CI]
	N (%) subjects	N events	N (%) subjects	N events	
All AEs					
Adverse events	157 (96.9%)	940	74 (96.1%)	341	0.8% [-12.7, 14.3]
SAEs	21 (13.0%)	26	4 (5.2%)	4	7.8% [-5.8, 21.2]
Related AEs					
AEs	134 (82.7%)	377	53 (68.8%)	94	13.9% [0.3, 27.2]
SAEs	6 (3.7%)	6	0 (0.0%)	0	3.7% [-9.9, 17.2]
Unrelated AEs					
AEs	129 (79.6%)	563	66 (85.7%)	247	-6.1% [-19.6, 7.5]
SAEs	18 (11.1%)	20	4 (5.2%)	4	5.9% [-7.6, 19.3]

Table 4-25: AEs through 12 Months by Investigator-Determined Severity

AE Severity	VBLOC		Sham Control		Difference [95% CI]
	N (%) subjects	N events	N (%) subjects	N events	
Any	157 (96.9%)	940	74 (96.1%)	341	0.8% [-12.7, 14.3]
Mild	150 (92.6%)	623	65 (84.4%)	212	8.2% [-5.5, 21.6]
Moderate	119 (73.5%)	272	59 (76.6%)	111	-3.2% [-16.7, 10.4]
Severe	27 (16.7%)	45	14 (18.2%)	18	-1.5% [-15.0, 12.1]

4.7.2 Serious Adverse Events (SAEs)

The SAE rate through 12 months was 13.0% in the VBLOC group and 5.2% in the sham control group. A breakdown of SAEs by the event origin as adjudicated by the CEC is shown in Table 4-26. Of the 26 SAEs with VBLOC, 6 were reports of nausea, 2 were related to gallbladder disease and 2 were due to other pain (Table 4-27).

Table 4-26: SAEs through 12 Months by CEC-Adjudicated Event Origin

SAE Origin	VBLOC		Sham Control	
	N (%) subjects	N events	N (%) subjects	N events
Device	3 (1.9%)	3	0 (0.0%)	0
Implant/revision procedure	2 (1.2%)	2	0 (0.0%)	0
Therapy algorithm	1 (0.6%)	1	0 (0.0%)	0
General surgical procedure	9 (5.6%)	9	0 (0.0%)	0
Other/Not related	4 (2.5%)	5	2 (2.6%)	2
Pre-existing condition	6 (3.7%)	6	2 (2.6%)	2

Table 4-27: All Related and Unrelated SAEs through 12 Months

SAE Type	VBLOC		Sham Control	
	N (%) subjects	N events	N (%) subjects	N events
Nausea	6 (3.7%)	6	0 (0.0%)	0
Gallbladder disease	2 (1.2%)	2	0 (0.0%)	0
Neuroregulator malfunction	2 (1.2%)	2	0 (0.0%)	0
Pain, other	2 (1.2%)	2	0 (0.0%)	0
Allergic reaction	1 (0.6%)	1	0 (0.0%)	0
Atelectasis	1 (0.6%)	1	0 (0.0%)	0
Chest pain	1 (0.6%)	1	0 (0.0%)	0
Cirrhosis	1 (0.6%)	1	0 (0.0%)	0
Colitis	1 (0.6%)	1	0 (0.0%)	0
Emesis/vomiting	1 (0.6%)	1	0 (0.0%)	0
Generalized ileus	1 (0.6%)	1	0 (0.0%)	0
Infection, other	1 (0.6%)	1	1 (1.3%)	1
Intra-operative oozing	1 (0.6%)	1	0 (0.0%)	0
Osteoarthritis	1 (0.6%)	1	0 (0.0%)	0
Pain, abdominal	1 (0.6%)	1	0 (0.0%)	0
Pain, neuroregulator site	1 (0.6%)	1	0 (0.0%)	0
Palpitations	1 (0.6%)	1	0 (0.0%)	0
Pericarditis	1 (0.6%)	1	0 (0.0%)	0
Gastritis	0 (0.0%)	0	1 (1.3%)	1
Right breast cancer	0 (0.0%)	0	1 (1.3%)	1
Worsening back pain	0 (0.0%)	0	1 (1.3%)	1

Between 12 and 18 months, there were six additional SAEs in the VBLOC group and one additional SAE in the sham control group. The additional SAE in the sham control group was

the onset of bladder cancer, which was related by the CEC to pre-existing condition. In the VBLOC group, there were three chest pain events, one infection event following an abscess removal and an event of worsening asthma that were all attributed to pre-existing condition.

One additional related SAE occurred between 12 and 18 months, for a related SAE rate of 4.3% (95% CI: 1.8 to 8.7) in the ITT population at 18 months. The additional related SAE was a gastric perforation that occurred in a female subject (307-313-RC) during explant of the device when she decided to discontinue study participation. The CEC event description from their adjudication report is provided below:

"A 29 year old woman with a past history of two C-sections, a cholecystectomy, a tubal ligation and uterine ablation had the placement of a neuroregulator on 12/14/2011. She elected to have the device removed and this was done as an outpatient on 2/12/2013. Overnight following the procedure she experienced increasing abdominal pain associated with nausea and vomiting. She presented to the emergency room on 2/13/2013 quite ill with marked abdominal pain, bilateral shoulder pain a systolic blood pressure of 87, a pulse of 116, a creatinine level of 3.2 and an abdominal CT scan showed a moderate amount of free fluid in the abdomen. She was taken to the OR where a 1.8 cm gastrotomy was identified at the gastroesophageal junction. The gastrotomy was repaired primarily and the area was reinforced with omentum which was sutured over the site of the gastrotomy repair. She remained mechanically ventilated overnight and required vasopresors to maintain her blood pressure. She improved post operatively. Her creatinine level returned to normal and she was extubated on 2/14/2013. She had a transient febrile episode on 2/15/2013. She continued to improve and was discharged to home on 2/18/2013."

The source documentation from the surgeon states that the perforation was on the anterior gastric wall near the gastroesophageal junction. This is the first occurrence of gastric perforation in over 640 implants of any generation of the Maestro System worldwide.

4.7.3 Primary Safety Endpoint

The primary safety endpoint, defined as the proportion of subjects in the treatment group who experience an implant/revision procedure, device, or therapy-related serious adverse event through 12 months post-implant, was 3.7% (95% CI, 1.4% to 7.9%) in the ITT population. This rate was significantly lower than 15% ($p<0.0001$), so the primary safety endpoint was met (Table 4-28). These SAEs are listed in Table 4-29.

Table 4-28: Primary Safety Endpoint in ITT Population

VBLOC Group Rate (95% CI) [n/N]	P-value (SAE Rate < 15%)
3.7% (1.4, 7.9) [6/162]	<0.0001

Table 4-29: SAE Listing for Primary Safety Endpoint in ITT Population

Subject ID	SAE Type	SAE Origin (Relatedness)
301-303-RC	Neuroregulator malfunction	Device (Definite)
301-325-RC	Pain, neuroregulator site	Device (Definite)
311-309-RC	Atelectasis	Implant/revision procedure (Definite)
311-319-RC	Neuroregulator malfunction	Device (Definite)
313-323-RC	Gallbladder disease	Therapy algorithm (Possible)
317-309-RC	Emesis (Vomiting)	Implant/revision procedure (Definite)

Although not the pre-specified primary safety endpoint, if the SAEs related to the general surgical procedure are included with the other related SAEs, the rate was 8.6% (95% CI: 4.8 to 14.1) at 12 months and 9.3% (95% CI: 5.3 to 14.8) at 18 months.

4.7.4 Adverse Events (AEs)

A summary of all AEs without attribution for relatedness are presented in Table 4-30. AEs that are likely related to VBLOC therapy, e.g., pain (other), heartburn/dyspepsia, abdominal pain, dysphagia, and belching, were more common in the VBLOC group.

Table 4-30: All AEs (Related and Unrelated) through 12 Months

AE Type	VBLOC		Sham Control		Difference [95% CI]
	N patients (%)	N events	N patients (%)	N events	
Other	90 (55.6%)	157	40 (51.9%)	62	3.6% [-10.0, 17.1]
Pain, other	81 (50.0%)	138	28 (36.4%)	36	13.6% [0.1, 26.9]
Cold/flu/respiratory tract infection	70 (43.2%)	121	33 (42.9%)	58	0.4% [-13.2, 13.9]
Pain, neuroregulator site	66 (40.7%)	79	32 (41.6%)	37	-0.8% [-14.3, 12.7]
Heartburn/dyspepsia	42 (25.9%)	46	4 (5.2%)	4	20.7% [7.2, 33.8]
Pain, abdominal	26 (16.0%)	33	2 (2.6%)	2	13.5% [-0.1, 26.7]
Constipation	24 (14.8%)	24	13 (16.9%)	15	-2.1% [-15.6, 11.5]
Headache	21 (13.0%)	24	8 (10.4%)	9	2.6% [-11.0, 16.1]
Out of range lab values	20 (12.3%)	23	6 (7.8%)	6	4.6% [-9.0, 18.0]
Nausea	17 (10.5%)	21	3 (3.9%)	3	6.6% [-6.9, 20.0]
Diarrhea	18 (11.1%)	19	4 (5.2%)	4	5.9% [-7.6, 19.3]
Infection, other	16 (9.9%)	19	12 (15.6%)	13	-5.7% [-19.2, 7.9]
Trauma	15 (9.3%)	19	11 (14.3%)	18	-5.0% [-18.5, 8.6]
Dysphagia	14 (8.6%)	14	1 (1.3%)	1	7.3% [-6.2, 20.8]
Emesis/vomiting	12 (7.4%)	13	6 (7.8%)	6	-0.4% [-13.9, 13.1]

AE Type	VBLOC		Sham Control		Difference [95% CI]
	N patients (%)	N events	N patients (%)	N events	
Eructation/belching	13 (8.0%)	13	0 (0.0%)	0	8.0% [-5.6, 21.4]
Incision pain, incision site	12 (7.4%)	13	7 (9.1%)	7	-1.7% [-15.2, 11.9]
Reaction to medicines	10 (6.2%)	12	6 (7.8%)	6	-1.6% [-15.1, 11.9]
Anxiety	11 (6.8%)	11	3 (3.9%)	3	2.9% [-10.6, 16.4]
Chest pain	11 (6.8%)	11	3 (3.9%)	4	2.9% [-10.6, 16.4]
Dizziness	10 (6.2%)	10	3 (3.9%)	3	2.3% [-11.3, 15.8]
Cramps, abdominal	7 (4.3%)	8	1 (1.3%)	1	3.0% [-10.6, 16.5]
Appetite increased	6 (3.7%)	7	3 (3.9%)	4	-0.2% [-13.7, 13.4]
Bloating, abdominal	7 (4.3%)	7	2 (2.6%)	3	1.7% [-11.8, 15.3]
Wound redness/irritation	7 (4.3%)	7	5 (6.5%)	5	-2.2% [-15.6, 11.4]
Energy, decreased	6 (3.7%)	6	1 (1.3%)	1	2.4% [-11.2, 15.9]
Hypertension	6 (3.7%)	6	3 (3.9%)	3	-0.2% [-13.7, 13.4]
Cardiac abnormality	5 (3.1%)	5	2 (2.6%)	2	0.5% [-13.1, 14.0]
Depression	5 (3.1%)	5	3 (3.9%)	3	-0.8% [-14.3, 12.7]
Edema	4 (2.5%)	4	0 (0.0%)	0	2.5% [-11.1, 16.0]
Respiratory abnormalities	4 (2.5%)	4	1 (1.3%)	2	1.2% [-12.4, 14.7]
Bleeding, other	3 (1.9%)	3	1 (1.3%)	1	0.6% [-13.0, 14.1]
Bradycardia	3 (1.9%)	3	0 (0.0%)	0	1.9% [-11.7, 15.4]
Gallbladder disease	3 (1.9%)	3	1 (1.3%)	1	0.6% [-13.0, 14.1]
Insomnia	3 (1.9%)	3	1 (1.3%)	1	0.6% [-13.0, 14.1]
Neuroregulator tilt	3 (1.9%)	3	0 (0.0%)	0	1.9% [-11.7, 15.4]
Psychosocial dysfunction	3 (1.9%)	3	1 (1.3%)	1	0.6% [-13.0, 14.1]
Skin reaction to coil/coil adhesion method	3 (1.9%)	3	0 (0.0%)	0	1.9% [-11.7, 15.4]
Urinary tract infection	3 (1.9%)	3	0 (0.0%)	0	1.9% [-11.7, 15.4]
Vitamin/mineral insufficiency	3 (1.9%)	3	2 (2.6%)	2	-0.7% [-14.3, 12.8]
Flatulence	2 (1.2%)	2	0 (0.0%)	0	1.2% [-12.3, 14.8]
Gastroesophageal reflux disease	2 (1.2%)	2	1 (1.3%)	1	-0.1% [-13.6, 13.5]
Infection, trocar site	2 (1.2%)	2	1 (1.3%)	1	-0.1% [-13.6, 13.5]
Neuroregulator malfunction	2 (1.2%)	2	0 (0.0%)	0	1.2% [-12.3, 14.8]
Palpitations	2 (1.2%)	2	0 (0.0%)	0	1.2% [-12.3, 14.8]
Paresthesia	2 (1.2%)	2	0 (0.0%)	0	1.2% [-12.3, 14.8]

AE Type	VBLOC		Sham Control		Difference [95% CI]
	N patients (%)	N events	N patients (%)	N events	
Swallowing pain	2 (1.2%)	2	0 (0.0%)	0	1.2% [-12.3, 14.8]
Syncope	2 (1.2%)	2	1 (1.3%)	1	-0.1% [-13.6, 13.5]
Allergic reaction	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Atelectasis	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Cirrhosis	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Colitis	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Cough	1 (0.6%)	1	1 (1.3%)	1	-0.7% [-14.2, 12.9]
Dehiscence, incision site	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Dehiscence, trocar site	1 (0.6%)	1	1 (1.3%)	1	-0.7% [-14.2, 12.9]
Delayed gastric emptying	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Dyspnea	1 (0.6%)	1	1 (1.3%)	1	-0.7% [-14.2, 12.9]
Generalized ileus	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Hypoglycemia	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Infection, neuroregulator site	1 (0.6%)	1	2 (2.6%)	2	-2.0% [-15.5, 11.6]
Intra-operative oozing	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Large bowel dysfunction	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Lightheadedness	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Osteoarthritis	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Pericarditis	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Seroma	1 (0.6%)	1	1 (1.3%)	1	-0.7% [-14.2, 12.9]
Dehiscence, neuroregulator site	0 (0.0%)	0	1 (1.3%)	1	-1.3% [-14.8, 12.3]
Gastritis	0 (0.0%)	0	1 (1.3%)	1	-1.3% [-14.8, 12.3]
Hematoma	0 (0.0%)	0	1 (1.3%)	1	-1.3% [-14.8, 12.3]
Right breast cancer	0 (0.0%)	0	1 (1.3%)	1	-1.3% [-14.8, 12.3]
Worsening back pain	0 (0.0%)	0	1 (1.3%)	1	-1.3% [-14.8, 12.3]

AEs determined by the investigator as related to the implant procedure, device or therapy are summarized in Table 4-31. The largest difference between VBLOC compared to sham control groups in related AEs was observed for events classified as pain (other), heartburn/dyspepsia, abdominal pain, dysphagia, and eructation/belching, which are likely due to sensations of therapy.

VBLOC therapy is delivered in a monopolar mode through two electrodes placed around the anterior and posterior vagal trunks adjacent to the esophagus. These electrodes function alternately as cathode and anode during delivery of the 5000 Hz current. Consequently, much

of the current flow between electrodes is through surrounding tissue, including structures such as the esophagus. During the initiation and increase in amplitude of VBLOC therapy, this current path may produce some visceral sensation by transient activation of nerve terminals or muscle in the immediate vicinity leading subjects to experience symptoms related to those structures. The AEs tend to be transient, associated with the timing of therapy and may improve over time.

Table 4-31: Related AEs through 12 Months

AE Type	VBLOC		Sham Control		Difference [95% CI]
	N (%) subjects	N events	N (%) subjects	N events	
Pain, neuroregulator site	61 (37.7%)	73	32 (41.6%)	35	-3.9% [-17.4, 9.7]
Other	34 (21.0%)	43	7 (9.1%)	10	11.9% [-1.7, 25.3]
Heartburn/dyspepsia	38 (23.5%)	42	3 (3.9%)	3	19.6% [6.0, 32.7]
Pain, other	37 (22.8%)	42	0 (0.0%)	0	22.8% [9.4, 35.8]
Pain, abdominal	20 (12.3%)	26	2 (2.6%)	2	9.7% [-3.8, 23.1]
Nausea	11 (6.8%)	14	1 (1.3%)	1	5.5% [-8.1, 19.0]
Dysphagia	13 (8.0%)	13	0 (0.0%)	0	8.0% [-5.6, 21.4]
Eructation/belching	13 (8.0%)	13	0 (0.0%)	0	8.0% [-5.6, 21.4]
Incision pain	12 (7.4%)	13	7 (9.1%)	7	-1.7% [-15.2, 11.9]
Chest pain	9 (5.6%)	9	2 (2.6%)	2	3.0% [-10.6, 16.5]
Cramps, abdominal	7 (4.3%)	7	0 (0.0%)	0	4.3% [-9.3, 17.8]
Wound redness or irritation	7 (4.3%)	7	5 (6.5%)	5	-2.2% [-15.6, 11.4]
Appetite increased	5 (3.1%)	6	2 (2.6%)	3	0.5% [-13.1, 14.0]
Constipation	6 (3.7%)	6	7 (9.1%)	7	-5.4% [-18.8, 8.2]
Emesis/vomiting	5 (3.1%)	6	2 (2.6%)	2	0.5% [-13.1, 14.0]
Bloating, abdominal	5 (3.1%)	5	1 (1.3%)	2	1.8% [-11.8, 15.3]
Headache	5 (3.1%)	5	2 (2.6%)	2	0.5% [-13.1, 14.0]
Diarrhea	4 (2.5%)	4	0 (0.0%)	0	2.5% [-11.1, 16.0]
Dizziness	3 (1.9%)	3	1 (1.3%)	1	0.6% [-13.0, 14.1]
Neuroregulator tilt	3 (1.9%)	3	0 (0.0%)	0	1.9% [-11.7, 15.4]
Out of range lab values	3 (1.9%)	3	0 (0.0%)	0	1.9% [-11.7, 15.4]
Skin reaction to coil/coil adhesion method	3 (1.9%)	3	0 (0.0%)	0	1.9% [-11.7, 15.4]
Bradycardia	2 (1.2%)	2	0 (0.0%)	0	1.2% [-12.3, 14.8]
Flatulence	2 (1.2%)	2	0 (0.0%)	0	1.2% [-12.3, 14.8]
Gastroesophageal reflux disease	2 (1.2%)	2	0 (0.0%)	0	1.2% [-12.3, 14.8]
Infection, trocar site	2 (1.2%)	2	1 (1.3%)	1	-0.1% [-13.6, 13.5]

AE Type	VBLOC		Sham Control		Difference [95% CI]
	N (%) subjects	N events	N (%) subjects	N events	
Neuroregulator malfunction	2 (1.2%)	2	0 (0.0%)	0	1.2% [-12.3, 14.8]
Swallowing pain	2 (1.2%)	2	0 (0.0%)	0	1.2% [-12.3, 14.8]
Atelectasis	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Cardiac abnormality	1 (0.6%)	1	1 (1.3%)	1	-0.7% [-14.2, 12.9]
Cirrhosis*	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Dehiscence, incision site	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Dehiscence, trocar site	1 (0.6%)	1	1 (1.3%)	1	-0.7% [-14.2, 12.9]
Depression	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Dyspnea	1 (0.6%)	1	1 (1.3%)	1	-0.7% [-14.2, 12.9]
Energy, decreased	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Gallbladder disease	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Generalized ileus	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Hypertension	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Hypoglycemia	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Infection, neuroregulator site	1 (0.6%)	1	2 (2.6%)	2	-2.0% [-15.5, 11.6]
Intra-operative oozing	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Lightheadedness	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Reaction to medicines	1 (0.6%)	1	1 (1.3%)	1	-0.7% [-14.2, 12.9]
Respiratory abnormalities	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Seroma	1 (0.6%)	1	1 (1.3%)	1	-0.7% [-14.2, 12.9]
Syncope	1 (0.6%)	1	0 (0.0%)	0	0.6% [-12.9, 14.2]
Bleeding, other	0 (0.0%)	0	1 (1.3%)	1	-1.3% [-14.8, 12.3]
Dehiscence, neuroregulator site	0 (0.0%)	0	1 (1.3%)	1	-1.3% [-14.8, 12.3]
Psychosocial dysfunction	0 (0.0%)	0	1 (1.3%)	1	-1.3% [-14.8, 12.3]
Trauma	0 (0.0%)	0	1 (1.3%)	1	-1.3% [-14.8, 12.3]

*Note that the cirrhotic event occurred in a subject who was not implanted due to a potential cirrhotic liver noted at implant. The subject had excessive bleeding during liver retraction and after the surgeon took liver biopsies to confirm disease presence. The CEC adjudicated the event related to general surgical procedure.

Detailed information about related AEs through 12 months in the VBLOC group are presented in Table 4-32, including severity, median time to onset, median duration, types of interventions, and the percentage of events that had resolved as of the 18-month data lock. Importantly, 98% of AEs related to VBLOC were mild to moderate in intensity and the large majority had resolved. Detailed information about related AEs in the sham control group through 12 months are presented in Table 4-33.

Table 4-32: Details of Related AEs in VBLOC Group through 12 Months

AE Type	N (%) Subjects	N events	Severity			Median (days)		Intervention			% Events Resolved
			Mild	Moderate	Severe	Time to Onset	Duration	Surgical	Medical/ Other	None	
Pain, neuroregulator site	61 (37.7%)	73	45	25	3	21	23	6	50	19	83.6%
Other	34 (21.0%)	43	39	3	1	30	19	0	17	26	79.1%
Heartburn/dyspepsia	38 (23.5%)	42	36	6	0	124	51	0	31	11	54.8%
Pain, other	37 (22.8%)	42	28	14	0	24	26	0	28	14	69.0%
Pain, abdominal	20 (12.3%)	26	17	9	0	78	22	1	22	4	88.5%
Nausea	11 (6.8%)	14	7	5	2	1	5	0	12	2	100.0%
Dysphagia	13 (8.0%)	13	12	1	0	7	25	0	3	10	76.9%
Eructation/belching	13 (8.0%)	13	13	0	0	11	88	0	2	11	69.2%
Incision pain	12 (7.4%)	13	12	1	0	0	22	0	9	4	100.0%
Chest pain	9 (5.6%)	9	8	1	0	32	4	0	4	5	66.7%
Cramps, abdominal	7 (4.3%)	7	2	5	0	202	16	0	6	1	42.9%
Wound redness or irritation	7 (4.3%)	7	6	1	0	23	16	0	5	2	100.0%
Appetite increased	5 (3.1%)	6	5	1	0	30	168	0	6	0	83.3%
Constipation	6 (3.7%)	6	6	0	0	13	7	0	4	2	83.3%
Emesis/vomiting	5 (3.1%)	6	3	2	1	15	1	1	4	2	100.0%
Bloating, abdominal	5 (3.1%)	5	4	1	0	13	12	0	2	3	80.0%
Headache	5 (3.1%)	5	4	1	0	6	1	0	5	0	60.0%
Diarrhea	4 (2.5%)	4	3	1	0	30	5	0	0	4	100.0%
Dizziness	3 (1.9%)	3	3	0	0	13	12	0	0	3	100.0%
Neuroregulator tilt	3 (1.9%)	3	3	0	0	14	19	1	3	0	66.7%

AE Type	N (%) Subjects	N events	Severity			Median (days)		Intervention			% Events Resolved
			Mild	Moderate	Severe	Time to Onset	Duration	Surgical	Medical/ Other	None	
Out of range lab values	3 (1.9%)	3	3	0	0	173	93	0	2	1	66.7%
Skin reaction to coil/coil adhesion method	3 (1.9%)	3	3	0	0	7	5	0	1	2	100.0%
Bradycardia	2 (1.2%)	2	1	1	0	123	119	0	0	2	50.0%
Flatulence	2 (1.2%)	2	2	0	0	87	74	0	0	2	100.0%
Gastroesophageal reflux disease	2 (1.2%)	2	2	0	0	335	163	0	2	0	100.0%
Infection, trocar site	2 (1.2%)	2	2	0	0	22	11	0	1	1	100.0%
Neuroregulator malfunction	2 (1.2%)	2	1	1	0	11	350	2	2	0	100.0%
Swallowing pain	2 (1.2%)	2	0	2	0	4	43	0	1	1	100.0%

Note: Only related AEs with more than one event are summarized. Resolution is based on a cut date of the 18-month data lock on November 11, 2013.

Table 4-33: Details of Related AEs in Sham Control Group through 12 Months

AE Type	N (%) Subjects	N events	Severity			Median (days)		Intervention			% Events Resolved
			Mild	Moderate	Severe	Time to Onset	Duration	Surgical	Medical/ Other	None	
Pain, neuroregulator site	32 (41.6%)	35	21	14	0	12	21	2	25	8	82.9%
Other	7 (9.1%)	10	6	3	1	15	18	1	8	2	90.0%
Constipation	7 (9.1%)	7	6	1	0	2	9	0	5	2	100.0%
Incision pain, incision site	7 (9.1%)	7	5	2	0	0	18	0	3	4	100.0%
Wound redness or irritation	5 (6.5%)	5	4	1	0	19	19	0	5	0	100.0%
Appetite increased	2 (2.6%)	3	2	1	0	145	103	0	3	0	100.0%
Heartburn/dyspepsia	3 (3.9%)	3	2	1	0	21	11	0	3	0	100.0%
Bloating, abdominal	1 (1.3%)	2	2	0	0	155	21	0	1	1	100.0%
Chest pain	2 (2.6%)	2	1	1	0	147	7	0	2	0	100.0%
Emesis/vomiting	2 (2.6%)	2	1	1	0	10	0	0	1	1	100.0%
Headache	2 (2.6%)	2	1	1	0	137	128	0	2	0	50.0%
Infection, neuroregulator site	2 (2.6%)	2	1	1	0	20	13	0	2	0	100.0%
Pain, abdominal	2 (2.6%)	2	2	0	0	75	232	0	1	1	100.0%

Note: Only related AEs with more than one event are summarized. Resolution is based on a data cut date of the 18-month data lock on November 11, 2013.

An update of related AEs through 18 months is shown in Table 4-34. The safety profile was similar that observed through 12 months. The vast majority of events were mild to moderate in severity, and most had resolved as of the 18-month data lock.

Table 4-34: Related AEs through 18 Months

AE Type	VBLOC				Sham Control			
	N (%) subjects	N events	% Resolved	Mild to Moderate	N (%) subjects	N events	% Resolved	Mild to Moderate
Pain, neuroregulator site	61 (37.7%)	76	83%	96%	32 (41.6%)	36	83%	100%
Pain, other	40 (24.7%)	48	71%	96%	0 (0.0%)	0	-	-
Other	37 (22.8%)	46	76%	98%	7 (9.1%)	10	90%	90%
Heartburn/dyspepsia	41 (25.3%)	45	56%	100%	3 (3.9%)	3	100%	100%
Pain, abdominal	22 (13.6%)	30	83%	100%	2 (2.6%)	2	100%	100%
Nausea	12 (7.4%)	17	94%	88%	1 (1.3%)	1	100%	100%
Eructation/belching	14 (8.6%)	14	71%	100%	0 (0.0%)	0	-	-
Incision pain	12 (7.4%)	14	100%	100%	7 (9.1%)	7	100%	100%
Chest pain	13 (8.0%)	13	69%	92%	2 (2.6%)	2	100%	100%
Dysphagia	13 (8.0%)	13	77%	100%	0 (0.0%)	0	-	-
Bloating, abdominal	7 (4.3%)	8	75%	100%	1 (1.3%)	2	100%	100%
Cramps, abdominal	8 (4.9%)	8	50%	100%	0 (0.0%)	0	-	-
Emesis/vomiting	6 (3.7%)	8	100%	88%	2 (2.6%)	2	100%	100%
Wound redness or irritation	8 (4.9%)	8	100%	100%	5 (6.5%)	5	100%	100%
Constipation	7 (4.3%)	7	86%	86%	7 (9.1%)	7	100%	100%
Appetite increased	5 (3.1%)	6	83%	100%	2 (2.6%)	3	100%	100%
Headache	6 (3.7%)	6	67%	100%	2 (2.6%)	2	50%	100%
Diarrhea	4 (2.5%)	4	100%	100%	0 (0.0%)	0	-	-
Out of range lab values	4 (2.5%)	4	50%	100%	0 (0.0%)	0	-	-
Dizziness	3 (1.9%)	3	100%	100%	1 (1.3%)	1	100%	100%
Neuroregulator tilt	3 (1.9%)	3	67%	100%	0 (0.0%)	0	-	-
Skin reaction to coil/coil adhesion meth	3 (1.9%)	3	100%	100%	0 (0.0%)	0	-	-
Bradycardia	2 (1.2%)	2	50%	100%	0 (0.0%)	0	-	-
Flatulence	2 (1.2%)	2	100%	100%	0 (0.0%)	0	-	-
Gastroesophageal reflux disease	2 (1.2%)	2	100%	100%	0 (0.0%)	0	-	-
Infection, trocar site	2 (1.2%)	2	100%	100%	1 (1.3%)	1	100%	100%
Neuroregulator malfunction	2 (1.2%)	2	100%	100%	0 (0.0%)	0	-	-
Seroma	2 (1.2%)	2	100%	100%	2 (2.6%)	2	0%	100%
Swallowing pain	2 (1.2%)	2	100%	100%	0 (0.0%)	0	-	-

AE Type	VBLOC				Sham Control			
	N (%) subjects	N events	% Resolved	Mild to Moderate	N (%) subjects	N events	% Resolved	Mild to Moderate
Atelectasis	1 (0.6%)	1	100%	100%	0 (0.0%)	0	-	-
Cardiac abnormality	1 (0.6%)	1	100%	100%	1 (1.3%)	1	100%	100%
Cirrhosis	1 (0.6%)	1	0%	100%	0 (0.0%)	0	-	-
Dehiscence, incision site	1 (0.6%)	1	100%	100%	0 (0.0%)	0	-	-
Dehiscence, neuroregulator site	1 (0.6%)	1	100%	100%	1 (1.3%)	1	100%	100%
Dehiscence, trocar site	1 (0.6%)	1	100%	100%	1 (1.3%)	1	100%	100%
Depression	1 (0.6%)	1	0%	100%	0 (0.0%)	0	-	-
Dyspnea	1 (0.6%)	1	100%	100%	1 (1.3%)	1	100%	100%
Energy, decreased	1 (0.6%)	1	100%	100%	0 (0.0%)	0	-	-
Gallbladder disease	1 (0.6%)	1	100%	0%	0 (0.0%)	0	-	-
Gastric perforation	1 (0.6%)	1	100%	0%	0 (0.0%)	0	-	-
Generalized ileus	1 (0.6%)	1	100%	100%	0 (0.0%)	0	-	-
Hypertension	1 (0.6%)	1	100%	100%	0 (0.0%)	0	-	-
Hypoglycemia	1 (0.6%)	1	100%	100%	0 (0.0%)	0	-	-
Infection, neuroregulator site	1 (0.6%)	1	100%	100%	2 (2.6%)	2	100%	100%
Intra-operative oozing	1 (0.6%)	1	100%	100%	0 (0.0%)	0	-	-
Lightheadedness	1 (0.6%)	1	100%	100%	0 (0.0%)	0	-	-
Neuroregulator migration	1 (0.6%)	1	0%	100%	0 (0.0%)	0	-	-
Reaction to medicines	1 (0.6%)	1	100%	100%	1 (1.3%)	1	100%	100%
Respiratory abnormalities	1 (0.6%)	1	0%	100%	0 (0.0%)	0	-	-
Syncope	1 (0.6%)	1	100%	100%	0 (0.0%)	0	-	-
Bleeding, other	0 (0.0%)	0	-	-	1 (1.3%)	1	100%	100%
Psychosocial dysfunction	0 (0.0%)	0	-	-	1 (1.3%)	1	100%	100%
Trauma	0 (0.0%)	0	-	-	1 (1.3%)	1	100%	100%

4.7.5 Adverse Events Associated with Study Withdrawal

In the VBLOC treatment group, one subject in the VBLOC group and three subjects in the sham control group withdrew due to an AE through 12 months. The subject who withdrew in the VBLOC group had pain at the neuroregulator site. All subjects who withdrew due to AEs through 12 months are summarized in Table 4-35 and subjects who withdrew between 12 and 18 months are summarized in Table 4-36.

Table 4-35: Adverse Events Leading to Study Withdrawal through 12 Months

Subject ID (Treatment Group)	AE Type (Relatedness)	Summary of Event
302-301-RC (VBLOC)	Pain, neuroregulator site (Related)	The subject was implanted on 08 SEP 2011. The subject reported an onset of severe pain at the neuroregulator site on 05 MAR 2012. Subject noted that she had jabbing pain when working out and other daily activities. The subject was explanted on 09 APR 2012 without complications.
302-304-RC (Sham Control)	Anxiety (Unrelated)	The subject was implanted on 08 SEP 2011. The subject reported an onset of worsened anxiety on 23 NOV 2011. The patient elected to withdraw from the study for psychological reasons. The subject was explanted on 09 APR 2012 and formally withdrawn on 18 APR 2012.
313-329-RC (Sham Control)	Breast cancer (Unrelated)	The subject was implanted on 14 DEC 2011. The subject reported that she had received a new diagnosis of right breast cancer on 06 APR 2012. The subject had a mastectomy at the time of device explant on 30 AUG 2012.
317-307-RC (Sham Control)	Pain, neuroregulator site (Related)	The subject was implanted on 19 OCT 2011. On 13 FEB 2012, the subject reported the onset of mild pain at the neuroregulator site, accompanied by increased tenderness and possible swelling, which began on 12 FEB 2012. The subject elected to have the device removed on 30 MAY 2012.

Table 4-36: Adverse Events Leading to Study Withdrawal between 12 and 18 Months

Subject ID (Treatment Group)	AE Type (Relatedness)	Summary of Event
302-302-RC (Sham Control)	Pain, other [rotator cuff] (Unrelated)	The subject was implanted on 08 SEP 2011. The subject reported an onset of pain in their rotator cuff on 04 JUN 2012, which required an MRI. The subject was explanted on 13 AUG 2012 so that MRI could be performed and was formally withdrawn on 23 AUG 2012.
303-315-RC (Sham Control)	Pain, neuroregulator site (Related)	The subject was implanted on 08 NOV 2011. The subject reported the onset of pain at the neuroregulator site on 22 JAN 2013 that accompanied weight loss. The subject was explanted on 04 MAR 2013 and was formally withdrawn on 18 MAR 2013.
313-309-RC (VBLOC)	Heartburn/ dyspepsia, Related	The subject was implanted on 19 OCT 2011. The subject reported an onset of heartburn/dyspepsia on 27 FEB 2012 that was reported on 20 AUG 2012. The subject stopped recharging their device prior to explant, and was ultimately explanted on 31 AUG 2012 and withdrawn on 07 JAN 2013.
313-327-RC (Sham Control)	Irritable bowel syndrome, worsening of symptoms (Related)	The subject was implanted on 14 DEC 2011. The subject reported worsening of IBS symptoms with a date of onset as of the day of implant surgery. The AE was attributed to therapy, (subject was in the sham control group and the study was still blinded). The subject was explanted on 24 JUL 2012 without complications.

4.7.6 Surgical Revisions

As shown in Table 4-37, 8 subjects (4.9%) in the VBLOC group had 9 surgical revisions performed: 5 (3.1%) for adverse events, 3 (1.9%) for device malfunction, and 1 subject (0.6%) for other reasons. One patient (304-307-RC) had their first revision on post-operative day 14 for an adverse event (neuroregulator pain) and had a subsequent revision on post-operative day 300 for device malfunction. Table 4-38 shows the reason and procedural outcome for subjects who underwent revision. There were no surgical revisions in the sham control group.

Table 4-37: Surgical Revision of Devices by Reason through 12 Months

Surgical Revision Reason	VBLOC		Sham Control	
	Revisions	N (%) subjects	Revisions	N (%) subjects
Adverse event	5	5 (3.1%)	0	0 (0.0%)
Device malfunction	3	3 (1.9%)	0	0 (0.0%)
Other	1	1 (0.6%)	0	0 (0.0%)
Overall	**9**	**8 (4.9%)**	**0**	**0 (0.0%)**

Table 4-38: Summary of Surgical Revisions through 12 Months

Subject ID (Treatment Group)	Reason for Revision	Description of Reason	Procedure Outcome
301-303-RC (VBLOC)	Adverse event	Related AE (Pain, neuroregulator site)	The subject was implanted on 27 JUN 2011. On 24 OCT 2011, the subject reported that the neuroregulator felt mobile with an associated date of onset of 17 OCT 2012. The neuroregulator had become detached, and was resutured on 09 DEC 2011. No implanted components were needed or changed. This resolved the pain.
301-325-RC (VBLOC)	Adverse event	Related AE (Pain, neuroregulator site)	The subject was implanted on 14 NOV 2011. On 21 FEB 2012, the subject reported pain and soreness at the neuroregulator site with an associated date of onset of 15 FEB 2012. The patient reported that the site was painful and the neuroregulator would catch under the ribs when gardening. The neuroregulator was repositioned on 22 OCT 2012. This resolved the pain.
301-326-RC (VBLOC)	Adverse event	Related AE (Neuroregulator tilt)	The subject was implanted on 16 NOV 2011. On 23 NOV 2011, the subject reported pain at the neuroregulator site, particularly a sharp pain when standing upright from gardening, with a date of onset of 21 NOV 2011. The neuroregulator was resutured on 14 DEC 2011. This resolved the tilt.

Subject ID (Treatment Group)	Reason for Revision	Description of Reason	Procedure Outcome
304-307-RC (VBLOC)	Adverse event	Related AE (Pain, neuroregulator site)	The subject was implanted on 04 NOV 2011. On 11 NOV 2011, the subject reported pain at the neuroregulator site and felt as if the device protruded/pressed on the abdominal wall. On 18 NOV 2011, the original neuroregulator position location was surgically revised, repositioned, and anchored to a more lateral position on 18 NOV 2011. This resolved the pain.
304-307-RC (VBLOC)	Device malfunction	The neuroregulator detected an abnormal condition and stopped delivering therapy	The neuroregulator was unable to deliver therapy due to a low impedance value in the posterior lead tip-to-ring circuit. The subject was implanted on 04 NOV 2011. The neuroregulator and posterior lead were surgically replaced on 30 AUG 2012 with new devices which were then connected with the existing anterior lead. Impedance values were in the normal range after the procedure and allowed for proper therapy delivery.
304-312-RC (VBLOC)	Device malfunction	The neuroregulator stopped communicating with the mobile charge	The communication issue was caused by a broken antenna connection in the neuroregulator header. The subject was implanted on 30 NOV 2011. The neuroregulator was surgically replaced on 22 FEB 2012 with a new device which was then connected to the existing anterior and posterior leads. The replacement of the neuroregulator resolved the communication issue, and allowed therapy delivery to resume.
304-323-RC (VBLOC)	Other	Neuroregulator tilt	The subject was implanted on 04 NOV 2011. The neuroregulator position was revised on 11 OCT 2012 and resutured in place. This resolved the tilt.
311-319-RC (VBLOC)	Adverse event	Related AE (Neuroregulator malfunction)	The neuroregulator was unable to communicate upon completion of the implant procedure. This was found to be due to a faulty transistor connector on the neuroregulator circuit board. The neuroregulator was surgically replaced on 01 FEB 2012 with a new device. The replacement of the neuroregulator resolved the communication issue.
317-313-RC (VBLOC)	Device malfunction	The neuroregulator detected an abnormal condition and stopped delivering therapy.	The neuroregulator was unable to deliver therapy due to a faulty transistor connection on the circuit board. The subject was implanted on 10 NOV 2011. The neuroregulator was surgically replaced on 14 APR 2012 with a new device which was then connected to the existing anterior and posterior leads. The replacement of the neuroregulator allowed therapy delivery to resume.

Between 12 and 18 months, there were an additional 3 revisions in 3 VBLOC subjects (Table 4-39). Two were for adverse events and one was for a device malfunction. Therefore, the 18-month revision rate was 6.8% in the VBLOC group and 0% in the sham control group.

Table 4-39: Summary of Surgical Revisions between 12 and 18 Months

Subject ID (Treatment Group)	Reason for Revision	Description of Reason	Procedure Outcome
301-324-RC (VBLOC)	Adverse event	Related AE (Pain, neuroregulator site)	The subject was implanted on 09 NOV 2011. The patient reported that in the morning she started to notice pain on top of the neuroregulator site and was tender to on 02 OCT 2012. The PI thought the neuroregulator had possibly dropped and was hitting on the ribs. At the 14-month visit, it was decided to resuture the device into place at a more anterior subcutaneous pocket, which was completed without incident 13 MAR 2013. The revision resolved the pain.
303-319-RC (VBLOC)	Adverse event	Related AE (Pain, neuroregulator site)	The subject was implanted on 21 NOV 2011. The patient reported discomfort when bending at the waist or lying on their stomach with a date of onset of 20 FEB 2013. The neuroregulator position was revised on 19 MAR 2013 and amplitude was reduced from 6.5 mA to 3 mA. The revision resolved the pain.
304-325-RC (VBLOC)	Device malfunction	The neuroregulator detected an abnormal condition and stopped delivering therapy	The neuroregulator was unable to deliver therapy due to a low impedance value in the ring- to-ring circuit. The subject was implanted on 22 DEC 2011. The subject had the neuroregulator and both the anterior and posterior leads surgically replaced 17 MAY 2013 following a radiograph that showed leads twisted and entwined in a manner consistent with Twiddler's Syndrome. After the procedure the lead impedance values have remained in normal range and allowed for therapy delivery.

4.7.7 Device Explants

There were 13 surgical explants of the device (Table 4-40) for the subjects who withdrew from the trial at or prior to completing the 12-month visit (8 in sham control and 5 in VBLOC). Eight of these subjects (7 sham control group, 1 VBLOC) were withdrawn from the study before their 12 month visit was completed, but five subjects (4 VBLOC group, 1 control group) were explanted before their 12-month visit but did not withdraw until after completing their 12-month visit. All surgical explants were completed without complication. All explanted subjects had a hospital stay of one day or less with the exception of one subject (313-329-RC) who had a mastectomy at the time of explant (Table 4-41).

There were two subjects in the VBLOC group (303-312-RC and 313-333-RC) who were lost to follow-up before the 12 month visit who did not have the device explanted.

Table 4-40: Surgical Explant of Device through 12 Months by Reason

Revision for Device Explant	VBLOC	Sham Control
Adverse event	2 (1.2%)	4 (5.2%)
Withdrawal from study/subject decision	3 (1.9%)	4 (5.2%)
Total	**5 (3.1%)**	**8 (10.4%)**

Table 4-41: Summary of Reasons for Surgical Removal of Device through 12 Months

Subject ID (Treatment Group)	Reason	Description of Reason
301-320-RC (Sham Control)	Withdrawal from study/subject decision	Subject was implanted on 31 OCT 2011. The subject was explanted on 20 AUG 2012 for cited reason of study fatigue.
302-301-RC (VBLOC)	Adverse event	Subject was implanted on 08 SEP 2011. The subject noted on 15 JAN 2012 that they had jabbing pain when doing physical activity. The subject was explanted on 09 APR 2012.
302-302-RC (Sham Control)	Adverse event	Subject was implanted on 08 SEP 2011. On 04 JUN 2012, patient noted pain in left shoulder that required an MRI, which required explant of device. The device was explanted on 13 AUG 2012.
302-304-RC (Sham Control)	Withdrawal from study/subject decision	Subject was implanted on 08 SEP 2011. The subject chose to leave the study for personal reasons and was explanted on 09 APR 2012.
304-324-RC (VBLOC)	Withdrawal from study/subject decision	Subject was implanted on 22 DEC 2011. The subject chose to leave the study for personal reasons and was explanted on 15 NOV 2012.
307-304-RC (VBLOC)	Withdrawal from study/subject decision	Subject was implanted on 14 OCT 2011. The subject chose to leave the study at the conclusion of the randomized follow-up period because of lack of efficacy. The device was explanted on 02 OCT 2012.
313-307-RC (VBLOC)	Withdrawal from study/subject decision	Subject was implanted on 12 OCT 2011. The subject did not recharge their device for several weeks and it could not be restarted. The explant was performed on 31 JUL 2012.
313-309-RC (VBLOC)	Adverse event	Subject was implanted on 19 OCT 2011. The subject reported on 20 AUG 2012 that they had been experiencing mild heartburn that was attributed by the investigator to therapy with an associated date of onset of 27 FEB 2012. The subject chose to stop recharging their device and the device was explanted on 31 AUG 2012.
313-327-RC (Sham Control)	Adverse event	Subject was implanted on 14 DEC 2011. The subject reported a worsening of IBS symptoms that they attributed to therapy of the device on 27 JUN 2012 with an associated date of onset on the date of implant. The subject was explanted on 24 JUL 2012 without complications.

Subject ID (Treatment Group)	Reason	Description of Reason
313-329-RC (Sham Control)	Adverse event	The subject was implanted on 14 DEC 2011. The subject reported that she had received a new diagnosis of right breast cancer on 06 APR 2012. The subject had a mastectomy at the time of device explant on 30 AUG 2012.
317-303-RC (Sham Control)	Withdrawal from study/subject decision	Subject was implanted on 14 OCT 2011. The subject chose to withdraw for personal reasons and was explanted on 22 FEB 2012.
317-307-RC (Sham Control)	Adverse event	The subject was implanted on 19 OCT 2011. On 13 FEB 2012, the subject reported the onset of mild pain at the neuroregulator site. The subject was explanted on 30 MAY 2012.
317-312-RC (Sham Control)	Withdrawal from study/subject decision	Subject was implanted on 10 NOV 2011. The subject was explanted on 25 JAN 2012 because an MRI was required to investigate symptoms of hepatitis and completed their trial exit visit on 21 FEB 2012.

There were 23 additional explants (14 VBLOC, 9 sham control) between 12 and 18 months (Table 4-42). Two explants in each group were due to adverse events; other explants were for subject decision. Therefore, the 18-month explant rate was 11.7% in the VBLOC group and 22.1% in the sham control group.

Table 4-42: Summary of Reasons for Surgical Removal of Device between 12 and 18 Months

Subject ID (Treatment Group)	Reason	Description of Reason
301-328-RC (Sham Control)	Adverse event	The subject was implanted on 07 DEC 2011. The patient reported worsening back and neck pain with an onset of 30 APR 3013, which required an MRI. The subject was explanted to undergo the MRI on 29MAY2013 and was subsequently withdrawn on 01JULY2013.
301-329-RC (VBLOC)	Adverse event	The subject was implanted on 09 DEC 2011. The subject reported worsening of right arm pain related to thoracic outlet syndrome with an onset of 20 JUN 2012, which required an MRI. The subject was explanted to undergo the MRI on 07JAN2013 and was formally exited from the study on 11APR2013.
302-313-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 03 NOV 2011. The patient elected to have their device explanted on 01 APR 2013 due to a failure to lose weight and was formally withdrawn from the study on 11 APR 2013.
302-315-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 30 NOV 2011. The patient elected to have their device explanted on 11 FEB 2013 due to a lack of efficacy and was formally withdrawn from the study on 27 FEB 2013.
303-315-RC (Sham Control)	Adverse event	The subject was implanted on 08 NOV 2011. The patient elected to have their device explanted on 04 MAR 2013 due to intermittent abdominal discomfort with movement at the neuroregulator site. The subject was formally withdrawn on 18 MAR 2013.

Subject ID (Treatment Group)	Reason	Description of Reason
303-326-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 16 DEC 2011. The patient elected to have their device explanted on 25 FEB 2013 due to a new job which would make it difficult to attend the required follow-up visits and lack of efficacy. The subject was explanted on 25 FEB 2013 and formally withdrawn on 25 FEB 2013.
304-301-RC (Sham Control)	Withdrawal from study/subject decision	The subject was implanted on 29 SEP 2011. The subject elected to have their device explanted in order to be converted to another bariatric procedure. The subject was explanted on 28 DEC 2012 and was formally withdrawn on 16 JAN 2013.
307-312-RC (Sham Control)	Withdrawal from study/subject decision	The subject was implanted on 06 DEC 2011. The patient elected to have their device explanted on 14 FEB 2013 due to subject decision. The subject was formally withdrawn on 03 MAY 2013.
307-313-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 14 DEC 2011. The patient elected to have their device explanted on 12 FEB 2013 due to lack of efficacy. The subject was formally withdrawn on 01 MAY 2013.
310-304-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 06 DEC 2011. The subject elected to have their device explanted on 28 JAN 2013 due to subject decision. The subject was formally withdrawn on 28 JAN 2013.
311-308-RC (Sham Control)	Withdrawal from study/subject decision	The subject was implanted on 07 NOV 2011. The subject elected to have their device explanted on 15 MAY 2013 due to subject decision. The subject was formally withdrawn on 07 JUN 2013.
311-309-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 14 NOV 2011. The subject elected to have their device explanted on 06 MAY 2013 due to subject decision. The subject was formally withdrawn on 19 JUN 2013.
311-310-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 14 NOV 2011. The subject elected to have their device explanted on 24 APR 2013 due to subject decision. The subject was formally withdrawn on 24 APR 2013.
311-313-RC (Sham Control)	Withdrawal from study/subject decision	The subject was implanted on 28 NOV 2011. The patient elected to have their device explanted on 15 MAY 2013 due to subject decision. The subject was formally withdrawn on 11 JUN 2013.
311-315-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 07 DEC 2011. The patient elected to have their device explanted on 25 FEB 2013 due to relocation away from the study center. The subject was formally withdrawn on 07 MAR 2013.
313-311-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 19 OCT 2011. The subject elected to have their device explanted on 05 MAR 2013 due to relocation away from the study center. The subject was formally withdrawn on 20 MAR 2013.
313-314-RC (Sham Control)	Withdrawal from study/subject decision	The subject was implanted on 02 NOV 2011. The subject elected to have their device explanted on 18 MAR 2013 due to subject decision. The subject was formally withdrawn on 04 JUN 2013.

Subject ID (Treatment Group)	Reason	Description of Reason
313-319-RC (Sham Control)	Withdrawal from study/subject decision	The subject was implanted on 16 NOV 2011. The subject elected to have their device explanted on 31 MAY 2013 in order to undergo another bariatric procedure. The subject was formally withdrawn on 25 JUN 2013.
313-320-R (VBLOC)	Adverse event	The subject was implanted on 16 NOV 2011. The subject reported the onset of abdominal pain in the right upper quadrant (rated 3 on a scale of 0 to 10) which was attributed by the investigator as related to the device on 12 NOV 2012. The subject elected to have their device explanted to resolve the abdominal pain on 04 DEC 2012 and was formally withdrawn on 30 AUG 2013.
313-325-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 30 NOV 2011. The subject elected to have their device explanted on 08 FEB 2013 due to subject decision. The subject was formally withdrawn on 23 SEP 2013.
313-332-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 26 DEC 2011. The subject elected to have their device explanted on 18 MAR 2013 due to subject decision. The subject was formally withdrawn on 30 AUG 2013.
315-327-RC (Sham Control)	Withdrawal from study/subject decision	The subject was implanted on 12 DEC 2011. The subject elected to have their device explanted on 18 MAR 2013 due to subject decision. The subject was formally withdrawn on 26 MAR 2013.
317-301-RC (VBLOC)	Withdrawal from study/subject decision	The subject was implanted on 14 OCT 2011. The subject elected to have their device explanted on 27 FEB 2013 in order to convert to another bariatric procedure. The subject was formally withdrawn on 25 MAR 2013.

5 MAXIMIZING PATIENT SAFETY POST-APPROVAL

EnteroMedics has given careful consideration to maximizing patient safety after PMA approval. Post-approval safeguards have been incorporated that include:

- A controlled launch with a limited number of users;
- Prerequisites for potential users and facilities;
- A training program that incorporates device and procedure training and careful review of the instructions for use;
- Post-approval vigilance that includes adverse event and device malfunction reporting;
- Long-term (5-year) post-approval follow up for subjects enrolled in ReCharge
- A post-marketing registry of newly enrolled subjects to gather real world experience in the United States.

EnteroMedics' proposal for following continued follow-up of ReCharge patients and the post-approval registry are described further in Section 7.0 of this document.

6 BENEFIT/RISK

ReCharge was a rigorously designed, randomized, double-blind, sham-controlled trial of VBLOC therapy using the Maestro Rechargeable System. Subjects in the ReCharge Study had a mean BMI of 40.9 and most had been obese since adolescence or childhood. All of the subjects in ReCharge had tried and failed more conservative weight loss interventions, such as diet, exercise and pharmacotherapy.

ReCharge was a well-executed study with 94% of randomized subjects remaining in the study through the first year. After 12 months of treatment, VBLOC subjects achieved an average 24.4% EWL (9.2% TBL) in the ITT population. The majority of VBLOC subjects achieved a clinically meaningful level of weight loss. At 12 months, 52% of VBLOC subjects achieved at least 20% EWL and 38% had at least 25% EWL. In terms of %TBL, 64% achieved at least 5% TBL and 36% achieved 10% TBL.

The ReCharge Study did not meet its pre-defined efficacy endpoints. However, the VBLOC group demonstrated significantly greater weight loss than the sham control in both average weight loss and in responder analyses despite a larger than anticipated sham response. Most importantly, weight loss for VBLOC subjects was shown to be durable through 18 months, while sham control subjects regained a large proportion of the weight they had lost at 12 months.

Supporting data from the ReCharge Study demonstrate the benefits of the weight loss obtained in the VBLOC group. Statistically significant reductions from baseline in obesity-associated risk factors including LDL cholesterol, triglycerides, systolic and diastolic blood pressure, heart rate and waist circumference were observed.

Data from landmark obesity studies such as DPP provide further supporting evidence for the clinical significance of the weight loss achieved in the VBLOC group. For example, DPP showed that 7% TBL at one year resulted in 58% reduction in the development of Type II diabetes in insulin resistant patients. This result was very similar to the 58.2% of VBLOC subjects who were considered pre-diabetic at baseline and improved to normal blood glucose levels at 12 months following treatment.

Similarly, statistically significant improvements in subjective measures, such as IWQoL-Lite and TFEQ and were observed at 12 months. The improvement in IWQoL-Lite demonstrates that the obese patients in ReCharge valued the benefits of weight loss and saw a noticeable improvement in their daily lives. Additional measures, such as the TFEQ, support the mechanism of action of vagal nerve blocking therapy since the results indicate that patients report feeling less hungry, allowing them to better control and manage their eating habits. These improvements remained durable for VBLOC subjects through 18 months while improvements in these measures for sham control subjects had begun to decline, consistent with the pattern observed with weight loss.

The majority of the AEs observed in the ReCharge Study were non-serious and most were unrelated to the device, procedure or therapy. AEs related to treatment with VBLOC therapy were mild to moderate in severity in 98% of cases, and most resolved with medical therapy or

no intervention. The most common related AEs reported were pain and GI symptoms, including heartburn, dysphagia, belching and nausea, which were typically easily managed and readily resolved. There is no evidence to suggest any damage to the vagus nerve in that there was no evidence of delayed gastric emptying. The 3.7% rate of SAEs related to the device, implant/revision procedure, or therapy at 12 months, which was considerably lower than the pre-specified 15% performance goal, provides additional evidence for the comparative safety of VBLOC therapy to current surgical weight loss options. Importantly, no SAEs were observed that are typical for other bariatric procedures, such as stricture, anastomotic leak, and device erosion.

The EMPOWER and VBLOC DM-2 studies provide supporting evidence of long-term safety of the Maestro System through 48 and 36 months, respectively. These studies demonstrate that adverse events remain infrequent and that there are no deaths or unanticipated adverse events. Patients in these studies continue to have weight loss over the 36 or 48 months for which data are available.

In conclusion, the ReCharge Study demonstrates an excellent safety profile for the Maestro Rechargeable System with a low occurrence of serious complications. Following FDA's new paradigm for obesity devices, this lower level of risk allows for a determination that a more modest treatment effect is acceptable. The Maestro Rechargeable System provides safe, durable, and clinically significant weight loss. Two-thirds of VBLOC subjects achieved clinically meaningful levels of 5% TBL or greater and the weight loss was shown to be durable through at least 18 months. Landmark clinical studies, such as DPP and LOOK AHEAD, as well as current clinical practice guidelines[22] support the clinical effectiveness of these levels of weight loss.

The ReCharge Study provides additional supporting evidence of the clinical benefits of the observed weight loss in the improvements of obesity risk factors, quality of life and the ability to control hunger and appetite. Considering the lower risk and the unmet public health need for new obesity therapies, the data in this PMA application provide a reasonable assurance that the benefits of the Maestro Rechargeable System for treating morbid obesity outweigh the risks of treatment with the device.

7 POST-APPROVAL STUDY

The purpose of the proposed post-approval program is to assess long term safety and efficacy of the Maestro Rechargeable System as well as to obtain real-world experience in using the Maestro system in a broader base of users.

7.1 LONG-TERM FOLLOW-UP OF RECHARGE SUBJECTS

The ReCharge Study is a 5-year clinical trial of the Maestro Rechargeable System and is the primary study supporting US FDA approval. Subjects randomized to the VBLOC arm and sham control patients who choose to be crossed over to an active Maestro Rechargeable System will be followed through 5-years post implant or crossover.

EnteroMedics proposes to use the 5-year data from subjects who were originally randomized to the VBLOC arm and crossover subjects from those originally randomized to the sham control group to support the long-term performance and safety of the Maestro Rechargeable System in the post-approval setting. Subjects who were randomized to the VBLOC arm will be followed through 5 years post-implant according to the study protocol. Patients who were randomized to the sham control group and elect to be crossed over to an active device will be followed for 5 years post-crossover procedure. All randomized VBLOC subjects will follow the visit schedule outlined in the ReCharge Study Clinical Investigation Plan, and crossover subjects will follow the 5-year visit schedule from the crossover implant. After the first year, subjects will be seen monthly through 2 years post-implant/crossover, and then every two months through 5 years.

At 18 months, 142 subjects randomized to the VBLOC arm were still enrolled in the study. Twelve (12) subjects randomized to the sham control arm had been crossed over to an active device by November 2013. It is assumed that approximately 30 to 40 sham control subjects will ultimately elect to be crossed over to an active device. We propose that the study sample to support the long-term efficacy of the Maestro Rechargeable System be comprised of these randomized VBLOC subjects and crossover subjects.

These subjects will be evaluated for long-term safety using a statistically-based hypothesis test. The primary safety objective of the extended follow-up will be to show that the rate of SAEs related to the device, implant/revision procedure, general surgical procedure, or therapy is statistically lower than 25% at 5 years. The performance goal of 25% was selected based on the 3-year rate of SAEs related to the device or procedure from the approval study for the FDA-approved REALIZE Adjustable Gastric Band, which was 25%.

The hypothesis test for the safety objective will be evaluated using the Kaplan-Meier estimate of the SAE rate at 5 years post-implant/crossover to account for expected attrition. Subjects will be censored at the time of their first related SAE or last available follow-up. The endpoint will be met if the upper 95% log-log confidence limit is lower than 25% at 5 years. Assuming a 25% performance goal, one-sided 0.05 type-I error rate, expected 5-year related SAE rate of 15%, and an 8% rate of censoring per year from implant/crossover, and the anticipated pooled

sample size of 162 randomized VBLOC subjects with 30-40 crossover subjects, it was estimated that the hypothesis would be powered at the 80% level.

The efficacy of the Maestro Rechargeable System will be assessed using mixed-effects regression models in the ITT sample. Both the estimated mean and 95% confidence intervals for %EWL and %TBL will be reported by visit using this methodology to reflect uncertainty for missing data. In addition to the mixed-effects model, data will be reported as observed without imputation. Weight loss will also be reported both pooled and stratified across original VBLOC randomized group versus crossover group.

Several strategies will be utilized to limit the amount of missing long-term data. The 5-year visit schedule was carefully planned not to be overly burdensome to make continued participation in the trial as easy as possible to ensure that subjects remained engaged in the study. EnteroMedics will continue to emphasize to investigators and study staff the importance of the completeness of long-term follow-up. In addition, both monetary and non-monetary incentives will be provided to subjects for completion of follow-up visits and completion of the full follow-up period. These incentives will be commensurate with the duration of follow-up and implemented in accordance with ethical requirements of institutional review boards.

Even with these efforts, EnteroMedics expects that the attrition in this study would be similar to that seen in recent trials of the adjustable gastric band. For example, the REALIZE Adjustable Gastric Band had a withdrawal rate of 48/276 (17.4%), or 5.8% attrition per year over three years. High drop-out rates are common in studies of obesity interventions. For example, the drop-out rates of approval studies for a recently approved obesity drug, lorcaserin, were 36% to 50% at one year. As a result, EnteroMedics has powered the study using an assumed 35-40% attrition rate, taking into consideration these reasons as well as the longer five-year duration of follow-up.

7.2 POST-MARKETING REGISTRY IN THE UNITED STATES

EnteroMedics plans to enroll new subjects in a Post-Marketing Registry as an open-label, single-arm study designed to gain additional experience with the Maestro Rechargeable system in the United States.

The objective of this observational study is to monitor the long-term safety profile of the Maestro Rechargeable system in the United States in the intended use population and to assess weight loss through 5 years post-implant.

EnteroMedics will be working closely with FDA to ensure an appropriate study design.

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