Clinical Investigational Plan

ReCharge Clinical Trial

Device: Maestro® Obesity Management System

Release: F
Date: 15April 2011

EnteroMedics Inc.
2800 Patton Road
St. Paul, MN 55113
USA

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<th>Title:</th>
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<td>IDE Number:</td>
<td>G070025/S038</td>
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<td>Device:</td>
<td>Maestro® Obesity Management System</td>
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<td>Release F</td>
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<td>USA</td>
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INVESTIGATOR’S AGREEMENT

By signing below I confirm that I have read this protocol and agree that it contains all necessary details for conducting this study. I will conduct the study according to the procedures described in this clinical investigational plan.

Principal Investigator’s Signature: ___________________________ Date

Principal Investigator’s Name (Print): ___________________________

SPONSOR’S AGREEMENT

______________________________________________________________

Katherine Tweden, PhD Date

Vice President of Research & Clinical Affairs
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1.0 Contact information

1.1 Principal investigator and co-investigators

The Sponsor will maintain a document with the contact information for all investigators and study personnel participating in the trial. The information maintained will include full name, degrees, addresses, telephone and fax numbers, and, if available, email addresses for the following:

- Principal investigator
- Co-investigator(s)
- Study coordinator(s)
- Clinic name
- Hospital name
- Institutional review board (IRB) chairperson

1.2 Sponsor

The information maintained and provided to each site from the sponsor will include full name, addresses, telephone and fax numbers, and email addresses for the following:

- Study Manager
- Field Clinical Engineer
- Clinical Monitor
- Local contacts, if any

If the contacts provided above cannot be reached please contact the following:

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2.0 Clinical investigational plan synopsis

| Background and rationale | The Maestro® Obesity Management System consists of a neuromodulation device that delivers intermittent, controllable electrical blocking algorithms, defined as VBLOC Therapy, to the intra-abdominal vagus nerves for the treatment of obesity. The Maestro System’s therapeutic rationale is based on principles supported by extensive clinical and preclinical published and unpublished data along with interim clinical trial safety and efficacy results on 322 subjects, including 294 from the US IDE EMPOWER clinical study with the RF2 System, and 28 from VBLOC-DM2 trial, an outside the United States feasibility trial utilizing the next generation RC2 system. The RC2 system will be studied in ReCharge.

  - The observations from the EMPOWER study include the following:
    - The safety profile of the device was excellent based on a low rate of Serious Adverse Events (SAEs) with no therapy-related SAEs and no electrocardiographic findings of concern.
    - No difference in efficacy was observed between control and treated subjects with regard to %EWL.
    - Confounding variables for hours of device use and an unanticipated indication of efficacy of control group parameters were observed.
    - Specifically, increased %EWL with increased hours of use was observed in both groups.
    - Clinically significant weight loss was observed in subjects using the device ≥ 9 hours per day.
  - The observations from the VBLOC-DM2 study include the following:
    - The observed weight loss was comparable to the ≥ 9 hours device use per day treated group from the EMPOWER study
    - The Maestro RC2 System mitigates the variable device use observed among the EMPOWER subjects.
    - The safety profile to date from the RC2 system feasibility trial is comparable to what was observed with the RF2 system from EMPOWER.
  - The efficacy results in the high use sub-group and safety profile of the EMPOWER trial and the efficacy observed from the RC2 system support further clinical development including initiation of a prospective, randomized controlled trial (ReCharge) using the Maestro RC2 System in patients with obesity who have not responded to more traditional weight loss treatments. |
## ReCharge Clinical Study overall aim

To determine the safety and efficacy of the Maestro RC2 System in producing weight loss in obese subjects

## Study design

- Prospective, randomized, double blind, parallel-group, multi-center trial to evaluate the safety and efficacy of the Maestro RC2 System in treating obesity.
- All subjects will receive an implanted device and will be randomized in a 2:1 allocation to treatment or control groups. The control group will have a non-active device that will deliver no charge to the vagus nerve as the comparison group.
- Note: Type 2 diabetics will be limited to 10% (no more than 3 subjects per center) of randomized subjects, and once the enrollment limit is reached, the centers will be notified and type 2 diabetic enrollments will stop.
- All subjects will participate in a weight management program, consisting of recommendations regarding diet, exercise, and behavior modification throughout the study.
- All subjects will receive blinded therapy through the 12-month follow-up visit, after which all subjects who were randomized to the control group will have the option to have a complete Maestro RC2 System implanted and receive therapy.

## Device tested

EnteroMedics Inc. is developing the Maestro® Obesity Management System, a medical device for the treatment of obesity. The Maestro RC2 System is a neuromodulation system that consists of the following implantable and external components.

1. **Implantable components:** two flexible leads (including one electrode each for the anterior and posterior intra-abdominal vagal nerve trunks) that are connected to an implantable neuroregulator placed subcutaneously on the thoracic sidewall in the area slightly anterior to the axial line and caudal to the axilla as the desired location, or in a location to be determined by the implanting surgeon. The leads are implanted laparoscopically and the neuroregulator is implanted in a subcutaneous pocket, similar to that used to implant a cardiac pacemaker.

2. **External components:** one mobile charger for the implanted neuroregulator, which is connected via a small, flexible cable to a cutaneous transmit coil that is positioned over the implanted neuroregulator when recharging the device or determining the status of the device; a software program on a laptop computer that transmits information to the neuroregulator and uploads data from the neuroregulator, which is available to the clinician, allowing both change in treatment regimens and assessment of battery recharging compliance.
**Objectives**

**Primary Efficacy Objective**
- To demonstrate at least 10% greater percentage of excess weight loss (% EWL) from randomization with the Maestro System after 12 months of VBLOC Therapy by BMI method
- A co-primary efficacy objective is to observe a responder rate in the treatment arm which will achieve the following:
  - at least 55% of subjects in the treated group achieve at least 20% EWL (by BMI) at 12 months.
  - at least 45% of the subjects in the treated group achieve at least 25% EWL (by BMI) at 12 months

Note: The co-primary efficacy objective is not statistically based.
Note: Both co-primary efficacy objectives must be met for trial success to be declared.

**Secondary Efficacy Objective**
- To demonstrate at least 10% greater percentage of excess weight loss (% EWL) from randomization with the Maestro System after 12 months of VBLOC Therapy by MetLife method

**Primary Safety Objective**
- To demonstrate a long-term (through 12 months), device-related SAE rate of less than 15%

**Supportive measurements and analyses**

**Safety**
- Long-term complications through 5 years
- 12 lead ECG
- Mortality and morbidity
- Pulse, blood pressure and body temperature
- Hemoglobin, hematocrit, platelet count and white blood cell count
- Serum sodium, potassium, chloride, bicarbonate, AST, ALT, alkaline phosphatase, blood urea nitrogen and creatinine, total bilirubin, uric acid, glucose, triglycerides, total cholesterol, HDL, LDL-calculated, calcium, phosphate, magnesium, iron, total iron-binding capacity (TIBC)
- Folic acid, vitamin B12, vitamin D, HbA1c, C-reactive protein

**Efficacy**
- Percentage of body weight loss
- Assessment of % EWL over 5 years
- Waist circumference/waist-hip ratio circumference
- Assessment of co-morbidities
  - Blood pressure
  - Gluco-regulation (HbA1c)
  - Lipoprotein profile

**Psychosocial**
- Quality of Life by:
  - Impact of Weight on Quality of Life Questionnaire-Lite (IWQOL-Lite)
- Depression assessment by Beck Depression Inventory (BDI®-II)
- Three Factor Eating Questionnaire (TFEQ)
- Hunger and appetite questionnaire
### Sample size

Approximately 234 obese subjects at up to 12 centers will be randomized. This is a sufficient number of study subjects to allow for a minimum of 198 evaluable subjects. Sample size is calculated using SAS V9.2 software (Proc Power) to compare two means. The minimum required sample size was calculated under the following assumptions:

- Significance level = 5%
- Power = 85%
- Expected difference (treatment-control) in % EWL = 20%
- Expected standard deviation = 22%
- Superiority margin = 10%
- 2:1 randomization allocation

Under the assumptions outlined above, the estimated minimum required sample size is 198 subjects (132 treatment group, 66 control group).

### Treatment groups

All subjects will receive an implanted device, weight management, and will be randomized in a 2:1 allocation to treatment or control groups for 12 months. After 12 months, all subjects randomized to the control group will have the option of a complete Maestro RC2 System implanted and receive therapy. All subjects will be followed for an additional 4 years in accordance with FDA’s post approval study requirements.

#### Weight management program (all subjects):

- 17 face-to-face sessions in the first 52 weeks after randomization
  - First session is 45 minutes
  - Second through fourth, are 30 minutes each
  - Remaining 13 sessions are 15 minutes each

#### VBLOC Therapy

- Treatment group: highest current amplitude (up to 8mA) with approximately 12 hours of therapy per day as acceptable to subject
- Control group: no therapy delivery

### Blinding

- The subject, sponsor (with the exception of specific sponsor personnel needed to support the safe use of the device), and clinical site follow-up staff will be blinded to treatment assignment
- Investigators and surgical support staff will not be blinded.
- Same study procedures for all subjects
- Device battery will deplete similarly in control and treatment groups
- Minimize subject interaction with other subjects in each subject’s first 12 months of the study

### Study population

#### Inclusion criteria

1. Signed informed consent
2. Body mass index (BMI) ≥ 40 kg/m² to 45 kg/m² or BMI ≥ 35 kg/m² to 39.9 kg/m² with one or more obesity related co-morbid conditions. Co-morbid conditions may include one or more of the following:
   - Type 2 diabetes mellitus as defined in inclusion criteria #5 (limited to 10% of randomized subjects)
   - Hypertension as defined by systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg
     - treated or untreated with systolic ≥140 mmHg or diastolic ≥90 mmHg
     - treated with systolic <140 mmHg and diastolic <90 mmHg
   - Dyslipidemia as defined by total cholesterol ≥200 or LDL ≥130
     - treated or untreated with total cholesterol ≥200 or LDL ≥130
     - treated with total cholesterol <200 or LDL <130
   - Sleep apnea syndrome (confirmed by overnight p02 studies)
   - Obesity-related cardiomyopathy
3. Females or males
   Note: females of child-bearing potential must have a negative urine pregnancy test at Screen and also within 14 days of implant procedure followed by physician-approved
contraceptive regimen for the duration of the study period.
4. 18-65 years of age inclusive.
5. Type 2 diabetes mellitus subjects:
   - Glycosylated hemoglobin (HbA1c) 7.0 - 10.0 % inclusive at screening visit.
     (Undiagnosed subjects that are found to have a HbA1c value between 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, liraglutide) for diabetes treatment and have not been on these treatments in the past 6 months.
   - Creatinine within normal reference range.
   - No history of proliferative retinopathy.
   - No history peripheral neuropathy.
   - No history of autonomic neuropathy.
   - No history of coronary artery disease, with or without angina pectoris.
   - No history of peripheral vascular disease.
6. Failure to respond to supervised diet/exercise program(s) in which the subject was engaged within the last five years.
7. Ability to complete all study visits and procedures.

Exclusion criteria
1. Concurrent chronic pancreatic disease.
2. History of Crohn’s disease and/or ulcerative colitis.
3. History of bariatric surgery, fundoplication, gastric resection or major upper-abdominal surgery (acceptable surgeries include cholecystectomy, hysterectomy).
4. History of pulmonary embolism or blood coagulation disorders.
5. 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.
6. Current cirrhosis, portal hypertension and/or esophageal varices.
7. Intra-operative exclusion: hiatal hernia requiring surgical repair or extensive dissection at esophagogastric junction at time of surgery.
8. 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.
9. Smoking cessation within the prior six months.
10. Known genetic cause of obesity (e.g., Prader-Willi Syndrome).
11. Weight loss of more than 10% of body weight in the previous 12 months.
12. Physician-prescribed diet with intent to lose weight prior to surgery (note: study subject may continue any personal eating plan they were on prior to study enrollment [see exclusion criterion #24])
14. Current or recent history (within 12 months) of ongoing bulimia.
15. Current alterations in treatment for thyroid disorders (stable treatment regimen for prior three months acceptable).
17. Current treatment for peptic ulcer disease (previous history acceptable).
18. Chronic (more than 4 weeks of daily use) treatment with narcotic analgesic drug regimens (treatment with non-steroidal anti-inflammatory drugs acceptable).
19. Current alterations in treatment regimens of anti-cholinergic drugs, including tricyclic antidepressants (stable treatment regimen for prior six months acceptable).
20. 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.
21. Presence of permanently implanted electrical powered medical device or implanted gastrointestinal device or prosthesis (e.g., pacemakers, implanted defibrillators, neurostimulators etc.).
22. Planned or contemplated use of Magnetic Resonance Imaging (MRI) or oncologic radiation during the course of the trial.
23. 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 will be considered to indicate severe depression.
24. Current, active member of an organized weight loss program (e.g., Weight Watchers, TOPS).
25. Current participant in another weight loss study or other clinical trials.
26. Have a friend or family member who is currently participating or is planning to participate in this clinical trial.
27. Patient reported:
   o inability to walk for about 10 minutes without stopping,
   o feeling of pain in chest when doing physical activity,
   o feeling of pain in chest when not doing physical activity.
Note: unless pain in chest in known to be related to upper gastrointestinal disorders such as gastroesophageal reflux disease or heartburn.
28. Clinically significant cardiac rhythm disorder that requires either medical and/or surgical intervention (e.g., paroxysmal or chronic atrial fibrillation).

### Study timeline overview (see schedule of trial events on table below)

- Screening period (informed consent, subject qualification, pre-operative testing)
- Randomization to treatment groups (2:1 treatment vs. control)
- Device implantation, initiation and pre-discharge check (possible one day hospitalization)
- Twelve months blinded follow-up period
  - Weekly visits for first month
  - Every two weeks between 4 weeks and 12 weeks
  - Monthly visits from three to 12 months
  - Telephone contact with subject once between scheduled visits from twelve weeks through 6 months
  - Following 12 month visit and unblinding, all subjects in the control group will have the option to have a complete Maestro RC2 System implanted and receive therapy. Subjects will be followed for an additional four years in accordance with FDA post approval study requirements as described below. The second year follow-up schedule for the control subjects who receive a fully functioning Maestro RC2 System will be identical to the first year follow-up schedule.
- Four-year open label follow-up in accordance with FDA post approval (PMA) requirements
  - Monthly visits from 12 to 24 months
  - Every two month visits from 24 to 60 months
  - Continuing weight management
Table 2.1 Schedule of trial events: Screen through 12 month follow-up

<table>
<thead>
<tr>
<th>Screening [Enrollment]</th>
<th>Randomization/Implant/Initiation</th>
<th>Week 1 Visit 7 ±3 days after Implant</th>
<th>Follow-up Visits 2, 3, 4, 6, 8, 10, 12 weeks (±3 days) 4, 5, 6, 7, 8, 9, 10, 11, 12 months (±14 days) after randomization</th>
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<tbody>
<tr>
<td>• Informed consent</td>
<td>• Body weight</td>
<td>• Subject self-assessment (optional)</td>
<td>• Subject self-assessment (optional)</td>
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<tr>
<td>• Inclusion/exclusion criteria assessments</td>
<td>• Vital signs</td>
<td>• Body weight</td>
<td>• Body weight</td>
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<tr>
<td>• Body weight</td>
<td>• Adverse event/medication use assessment</td>
<td>• Vital signs</td>
<td>• Vital signs*</td>
</tr>
<tr>
<td>• Body height</td>
<td>• Randomized to treatment groups</td>
<td>• Adverse event / medication use assessment</td>
<td>• Adverse event/medication use assessment</td>
</tr>
<tr>
<td>• Vital signs*</td>
<td>• Device implant (after all procedures above)</td>
<td>• Device training</td>
<td>• Physical exam if needed</td>
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<tr>
<td>• Medication use assessment</td>
<td></td>
<td>• 7 day diet and activity diary</td>
<td>• Clinical laboratory assessments (6 &amp;12 months)</td>
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<tr>
<td>• Psychological assessment</td>
<td></td>
<td>• Blinding status</td>
<td>• Waist and hip circumferences (12 months)</td>
</tr>
<tr>
<td>• Waist and hip circumferences</td>
<td></td>
<td>• Weight management</td>
<td>• Weight management</td>
</tr>
<tr>
<td>• Clinical laboratory assessments</td>
<td></td>
<td>• Device management</td>
<td>• Device interrogation</td>
</tr>
<tr>
<td>• Subject Questionnaires</td>
<td></td>
<td>• 12 lead ECG</td>
<td>• Current amplitude adjustments as indicated</td>
</tr>
<tr>
<td>• Physical exam</td>
<td></td>
<td>• Preoperative assessments (upper GI xray or upper endoscopy)</td>
<td>• Assess/maximize compliance with recharging</td>
</tr>
<tr>
<td>• 7 day diet and activity diary</td>
<td></td>
<td>• Device overview and training</td>
<td>• 12 lead ECG (4, 8, 12 months)</td>
</tr>
<tr>
<td>• 12 lead ECG</td>
<td></td>
<td></td>
<td>• 7 day diet and activity diary</td>
</tr>
<tr>
<td>• Preoperative assessments (upper GI xray or upper endoscopy)</td>
<td></td>
<td></td>
<td>• Blinding status (6 &amp; 12 mo)</td>
</tr>
<tr>
<td>• Device overview and training</td>
<td></td>
<td></td>
<td>• Subject Questionnaires (3, 6 &amp; 12 mo)</td>
</tr>
<tr>
<td>• Telephone contact with subject between visits (12 week-6 months)</td>
<td></td>
<td></td>
<td>• Telephone contact with subject between visits (12 week-6 months)</td>
</tr>
</tbody>
</table>

* Blood pressure collected in triplicate at screening, implant, months 3, 6, 9, and 12 month visits.
### Table 2.2 Schedule of trial events: 12 months through 60 months follow-up

| Follow-up Visits | 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60 months (±14 days) after randomization*

- Subject self-assessment (optional)
- Body weight
- Vital signs*
- Adverse event/medication use assessment
- Clinical laboratory assessments
  (24, 36, 48 and 60 months)
- Waist and hip circumferences
  (24, 36, 48, and 60 months)
- Weight management
  (Individual at all visits and group quarterly)
- Device interrogation
- Current amplitude adjustments as indicated
- Assess/maximize compliance with recharging
- Subject Questionnaires
  (18, 24, 30, 36, 42, 48, 54, and 60 months)
- * Blood pressure collected in triplicate at 18, 24, 30, 36, 42, 48, 54, and 60 months visits.
-  Once control group subjects receive a fully functioning device, they will be seen according to the year one follow-up schedule for the next 12 months.
3.0 Preliminary investigations and justification of the trial

3.1 Introduction

The Maestro® Obesity Management System consists of a neuromodulation device that delivers intermittent, controllable electrical blocking algorithms, defined as VBLOC Therapy, to the intra-abdominal vagus nerve for the treatment of obesity. The Maestro System is a neuromodulation system that consists of the following implantable and external components.

- **Implantable components:** two flexible leads (including one electrode each for the anterior and posterior intra-abdominal vagal nerve trunks) that are connected to an implantable neuroregulator placed subcutaneously on the thoracic sidewall in the area slightly anterior to the axial line and caudal to the axilla as the desired location, or in a location to be determined by the implanting surgeon. The leads are implanted laparoscopically and the neuroregulator is implanted in a subcutaneous pocket, similar to that used to implant a cardiac pacemaker.

- **External components:** one mobile charger for the implanted neuroregulator, which is connected via a small, flexible cable to a cutaneous transmit coil that is positioned over the implanted neuroregulator when charging the device or determining the status of the device; a software program on a laptop computer that transmits information to the neuroregulator and uploads data from the neuroregulator, which is available to the clinician, allowing both change in treatment regimens and assessment of treatment.

3.2 Therapeutic need and opportunity in the treatment of obesity

- Obesity is a global medical concern.

  - In the United States, published estimations 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.¹

  - Two out of every three (65.7%) adults in the U.S. are either obese (BMI ≥ 30.0 kg/m²) or overweight (BMI 25.0-29.9). One in twenty people in the U.S. is categorized as extremely obese (BMI ≥ 40).²

  - Recent studies document the morbidity and mortality associated with BMI over 35, as well as the potential benefits accruing to patients with obesity-related co-morbid diseases once substantial weight loss is achieved.³,⁴

  - The prevalence of children and adolescents who are overweight has increased more than two-fold since 1976.⁵

  - There is a well-established association between obesity and clinically important diseases, e.g., type 2 diabetes, hypertension and osteoarthritis – three leading causes of morbidity and mortality in industrialized countries.⁶
The currently available treatment options do not meet the needs of many obese patients.\(^7\)

Patients who are obese incur 37% more health care costs than people with normal weight, and spending on obese patients accounted for 27% of the growth in inflation-adjusted per capita health care spending between 1987 and 2001.\(^8\)

The public health and therapeutic challenges posed by obesity continue to be the focus of treatment guidelines.\(^9,10\)

Finding a successful obesity treatment continues to challenge both health care providers and patients. Diet and exercise programs may result in short-term weight loss but are associated with slow, inexorable weight regain for most people.\(^7\)

Drug therapy has also resulted in variable success and weight loss for the obese patient population. A meta-analysis has yielded the following treatment results.\(^10\)

- **bupropion**: 2.8 kg loss at 6-12 months
- **diethylpropion**: 3.0 kg loss at 6 months
- **fluoxetine**: 3.15 kg loss at 12 months
- **orlistat**: 2.89 kg loss at 12 months
- **phentermine**: 3.6 kg loss at 6 months
- **sibutramine**: 4.45 kg loss at 12 months

Death or other serious adverse events – sometimes resulting in bold-font warning statements in the prescribing information\(^11\) – have been reported. In fact, in cases such as “fen-phen” (fenfluramine-phentermine) and “PPA” (phenylpropanolamine), removal from the market has occurred. In addition, sibutramine has recently been contraindicated for use in patients with a history of cardiovascular disease.\(^12\)

Bariatric surgery has been done since the 1960s. Roux-en-Y gastric bypass (RYGBP) is the most common procedure in the U.S., and the prevalence of gastric banding is increasing. In 2003, the number of bariatric procedures had reached 103,000, and 144,000 such procedures were projected by the end of 2004. In 2008, the number of bariatric procedures was 220,000.\(^13,14,15,16\) RYGBP results in the greatest and most sustained weight loss but is also associated with substantial short- and long-term morbidity and mortality, with 30-day mortality rates reported to range from below 1.0% to 1.9% or more depending on the experience of the surgeon and the annual number of procedures performed at the hospital.\(^17,18,19\) Gastric banding, is also effective but results in significantly less weight loss, both short- and long-term, than the RYGBP operation.\(^20\)

### 3.3 Anatomy and physiology of the vagus nerve

The tenth cranial nerve, the vagus nerve,\(^21,22\) originates in the brain and is the longest of the twelve cranial nerves. In fact, the vagus can be thought of as the “spinal cord” of the autonomic nervous system. Together with three sacral nerves, the vagus nerve is the principal pathway for parasympathetic nervous system communication to and from the brain. Vagal efferent nerve transmission (from the brain to the body) regulates a broad
range of physiologic functions. Furthermore, vagal afferent fibers (from the body to the brain) comprise approximately 80% of the fibers of the vagus nerve. The vagus nerve has the most extensive distribution of all the cranial nerves modulating many essential physiologic functions involved in nutrient ingestion, processing and digestion, including the following functions relevant to this approach to treating obesity.

- Stomach: post-prandial gastric volume (accommodation/receptive relaxation), gastric contractions (food processing), acid secretion and gastric emptying
- Pancreas and gall bladder: pancreatic exocrine secretion, gallbladder emptying and bile flow
- Visceral (intra-abdominal) organ sensitivity: modulation of sensations of satiation, satiety (hunger), nausea, dull pain and discomfort
- Small intestine: intestinal motility and intestinal content transit

3.4 Interim clinical results of VBLOC therapy from EMPOWER and VBLOC-DM2 clinical trials

3.4.1 EMPOWER clinical trial design

The EMPOWER trial was a randomized, double-blind, controlled, parallel group, multi-center trial with a 12 month post-randomization blinded follow-up period. All subjects received all implantable components of the Maestro system at the time of implantation. At the end of the blinded follow-up period, all subjects receive open-label VBLOC Therapy and are followed for four additional years.

Study objectives:

- **Primary safety objective**
  To estimate the rate of serious, system- and procedure-related adverse events associated with the Maestro System.

- **Secondary safety objective**
  To estimate the rate of serious, therapy-related adverse events.

- **Primary efficacy objective**
  To demonstrate a significantly greater percentage of excess weight loss (% EWL) with the Maestro System after 12 months of VBLOC Therapy.

- **Secondary efficacy objective**
  To demonstrate a significant difference between treatment groups in the proportion of subjects realizing at least a 25% EWL from implant at 12 months post-randomization.

Investigational device overview

The Maestro RF2 System is a neuromodulation system that consists of implantable and external components. The implantable components include two leads (including one
each for the anterior and posterior intra-abdominal vagal nerve trunks) that are connected to an implantable neuroregulator placed subcutaneously. The external components include one battery-powered external controller connected to a cutaneous transmit coil that is positioned over the implanted neuroregulator. The device also includes a software program on a laptop computer that transmits information to the controller.

Because the external controller holds the external battery, subjects are required to position the transmit coil over the implanted neuroregulator in order for therapy to be delivered. The desired target time for wearing the device (as described in the protocol and informed consent document) was 9 to 16 hours per day. Although patients were encouraged by the study investigators and coordinators to wear the device as much as possible, the decision whether or not to wear the device was solely under the patient’s control.

### Treatment groups:

**Treated group**
- Highest VBLOC Therapy current amplitude (3 to 8mA) efficacious and acceptable to subject
- Impedance and associated device safety and diagnostic checks during therapy algorithm cycles

**Control group**
- VLBOC Therapy current amplitude set to 0mA
- Impedance and associated device safety and diagnostic during therapy algorithm cycles

### Randomization:

2:1 Treated group to control group
1:1 Treated group to control group for subjects with type 2 diabetes mellitus

### Study methods

After finishing the informed consent process, all potential subjects completed the screening period procedures to determine eligibility for implant. Eligible subjects were implanted. Seven to 21 days after device implantation subjects were randomized to one of two treatment groups and had the device activated to begin either blinded VBLOC Therapy or control mode. It is important to note that the device was operational in both groups and energy was delivered to the vagus nerve in both the treated group and the control group. Impedance, device safety, and device diagnostic checks were performed and compliance data were collected in both groups. To perform these checks, charge was delivered to the vagus nerve. For these safety checks to occur, the device had to be powered using the transmit coil. However, as previously described, in addition to the safety checks, the device was programmed to deliver 3 to 8 mA of VBLOC Therapy current in the treated group and 0 mA of VBLOC Therapy current in the control group. The control-mode device safety checks were performed every 25 ms during the five minute ON time cycle in the control group.
At 7 to 21 days after device implantation, all subjects also began the weight management program. Subjects were then followed for 12 months during routine follow-up visits.

3.4.2 EMPOWER Clinical Trial Results

294 subjects were enrolled and implanted in a prospective, randomized, double-blind, placebo-controlled, multi-center clinical trial. The average subject was approximately 45.7 years of age and Caucasian (90.0% of the total population), and the majority of subjects in each treatment group were female (88.6% of the total population). Mean BMI at implant was 41.1±2.7 kg/m² and mean BMI at randomization (initiation) was 40.5±2.7 kg/m². Baseline demographics between the two treatment arms are comparable. There were no differences seen between treatment groups in baseline medical history, surgical history, time of onset of obesity, tobacco use status, and/or concomitant medication use.

3.4.3 EMPOWER Clinical Trial Safety

The Clinical Event Committee (CEC) reviewed and adjudicated all serious adverse events (SAEs) through 12 months. There were no deaths or UADEs in the EMPOWER trial. Among all 294 implanted and randomized subjects, 35 SAEs occurred and were adjudicated by the CEC as shown in Table 3.1. All SAEs by event type are provided in Table 3.2.

Table 3.1. All serious adverse events (SAE) by CEC-Adjudicated event origin –All subjects (includes surgical roll-in subjects)

<table>
<thead>
<tr>
<th>Relatedness (Event Origin)</th>
<th>Treated N=192</th>
<th>Control N=102</th>
<th>Difference (95% CI)</th>
<th>Overall N=294</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgical procedure</td>
<td>4 (2.1%)</td>
<td>0 (0.0%)</td>
<td>2.1% (-9.9, 14.1)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>Implant/revision procedure</td>
<td>3 (1.6%)</td>
<td>2 (2.0%)</td>
<td>-0.4% (-12.4, 11.6)</td>
<td>5 (1.7%)</td>
</tr>
<tr>
<td>Device</td>
<td>3 (1.6%)</td>
<td>1 (1.0%)</td>
<td>0.6% (-11.4, 12.6)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>Therapy algorithm</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>NA</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pre-existing condition</td>
<td>9 (4.7%)</td>
<td>8 (7.8%)</td>
<td>-3.2% (-15.1, 8.9)</td>
<td>17 (5.8%)</td>
</tr>
<tr>
<td>Other/not related</td>
<td>4 (2.1%)</td>
<td>1 (1.0%)</td>
<td>1.1% (-10.9, 13.1)</td>
<td>5 (1.7%)</td>
</tr>
</tbody>
</table>

*Note: one additional SAE (CEC-adjudicated as general surgical procedure) in a non-implanted, non-randomized subject is not included in the comparison of randomized subjects above and is not included in the Overall SAE count.
Table 3.2. All serious adverse events by event type – All subjects (includes surgical roll-in subjects)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Treated N=192</th>
<th>Control N=102</th>
<th>Difference (95% CI)</th>
<th>Overall N=294</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding other (specify)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.5% (-11.7, 12.8)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Bronchospasm1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiac abnormality</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.5% (-11.7, 12.8)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Cold/flu/respiratory tract infection</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.5% (-11.7, 12.8)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.5% (-11.7, 12.8)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0.0%)</td>
<td>1 (1.0%)</td>
<td>-1.0% (-13.3, 11.2)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Incision pain incision site</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.5% (-11.7, 12.8)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Infection neuroregulator site</td>
<td>2 (1.1%)</td>
<td>1 (1.0%)</td>
<td>0.1% (-12.2, 12.3)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Infection other (specify)</td>
<td>1 (0.5%)</td>
<td>1 (1.0%)</td>
<td>-0.5% (-12.4, 11.5)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Large bowel dysfunction</td>
<td>0 (0.0%)</td>
<td>1 (1.0%)</td>
<td>-1.0% (-13.3, 11.2)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Lead impedance high</td>
<td>0 (0.0%)</td>
<td>1 (1.0%)</td>
<td>-1.0% (-13.3, 11.2)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Neuroregulator malfunction</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.5% (-11.7, 12.8)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (4.4%)</td>
<td>6 (6.2%)</td>
<td>-1.8% (-14.0, 10.5)</td>
<td>14 (4.8%)</td>
</tr>
<tr>
<td>Pain abdominal</td>
<td>3 (1.6%)</td>
<td>0 (0.0%)</td>
<td>1.6% (-10.6, 13.9)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Pain neuroregulator site</td>
<td>1 (0.5%)</td>
<td>1 (1.0%)</td>
<td>-0.5% (-12.7, 11.8)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Pain other (specify)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.5% (-11.7, 12.8)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Reaction to medicines</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.5% (-11.7, 12.8)</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

1One additional SAE, bronchospasm (CEC-adjudicated as general surgical procedure) in a non-implanted, non-randomized subject is not included in the comparison of randomized subjects above.

The DSMB reviewed all group 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 treated or control groups from EMPOWER. Heart rate was observed to decrease slightly relative to baseline equally in both groups, a finding consistent with the weight loss observed.

3.4.4 EMPOWER clinical trial efficacy

As shown below, the primary (Table 3.3) and secondary (Table 3.4) efficacy endpoints were not met.

In reference to Table 3.5, over 30% of subjects in both groups achieved 20% EWL. Weight losses of approximately 20% EWL (about 10% body weight) have been demonstrated to result in substantial clinically important improvements in obesity-related
co-morbidities such as diabetes, hypertension, sleep apnea and dyslipidemia compared to baseline and reported in randomized, placebo controlled trials. 23, 24, 25, 26, 27, 28, 29

Table 3.3. Primary efficacy endpoint: %EWL (MetLife method) at 12 months from initiation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treated</th>
<th>Control</th>
<th>Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>165</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>-12.1±17.5</td>
<td>-12.0±20.8</td>
<td>-0.1±18.7</td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(-74.8, 18.9)</td>
<td>(-101, 20.3)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
</tbody>
</table>

Table 3.4. Secondary efficacy: Subjects achieving 25% or more EWL (BMI method) from implant at 12 months

<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Control</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25% EWL from Implant</td>
<td>41 (22.4%)</td>
<td>24 (24.7%)</td>
<td>-2.3 (-14.6, 9.9)</td>
</tr>
</tbody>
</table>

Table 3.5. Percent of subjects who completed 12 months achieving varying levels %EWL (BMI method) from implant at 12 months

<table>
<thead>
<tr>
<th>Percent EWL (BMI method) Achieved</th>
<th>Treated N=165</th>
<th>Control N=88</th>
<th>Difference (95% CI)</th>
<th>Overall N=253</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% EWL from Implant</td>
<td>102 (61.8%)</td>
<td>43 (48.9%)</td>
<td>13.0 (-0.0, 25.6)</td>
<td>57.3%</td>
</tr>
<tr>
<td>15% EWL from Implant</td>
<td>69 (41.8%)</td>
<td>36 (40.9%)</td>
<td>0.9 (-12.0, 13.8)</td>
<td>41.5%</td>
</tr>
<tr>
<td>20% EWL from Implant</td>
<td>54 (32.7%)</td>
<td>29 (33.0%)</td>
<td>-0.2 (-13.1, 12.7)</td>
<td>32.8%</td>
</tr>
<tr>
<td>25% EWL from Implant</td>
<td>41 (24.8%)</td>
<td>24 (27.3%)</td>
<td>-2.4 (-15.3, 10.5)</td>
<td>25.7%</td>
</tr>
<tr>
<td>30% EWL from Implant</td>
<td>30 (18.2%)</td>
<td>23 (26.1%)</td>
<td>-8.0 (-20.7, 5.0)</td>
<td>20.9%</td>
</tr>
<tr>
<td>35% EWL from Implant</td>
<td>23 (13.9%)</td>
<td>12 (13.6%)</td>
<td>0.3 (-12.6, 13.2)</td>
<td>13.8%</td>
</tr>
<tr>
<td>40% EWL from Implant</td>
<td>19 (11.5%)</td>
<td>10 (11.4%)</td>
<td>0.2 (-12.8, 13.1)</td>
<td>11.5%</td>
</tr>
<tr>
<td>45% EWL from Implant</td>
<td>14 (8.5%)</td>
<td>8 (9.1%)</td>
<td>-0.6 (-13.5, 12.3)</td>
<td>8.7%</td>
</tr>
<tr>
<td>50% EWL from Implant</td>
<td>11 (6.7%)</td>
<td>7 (8.0%)</td>
<td>-1.3 (-14.2, 11.7)</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

There were no differences observed between treatment arms in device compliance (defined as hours of device use), average hours of therapy per day, and therapy algorithm settings. However, both average hours of use per day and total therapy days showed
positive and statistically significant associations with %EWL from baseline with greater hours of device use per day. This finding was observed regardless of treatment arm.

When looking at %EWL by average hours of use per day categories (Figure 3.1), a clear relationship of greater weight loss with increasing average hours of use per day is observed. A similar relationship is observed in both groups, although there appears to be at least a trend towards greater weight loss in the treatment group when the device was worn for \( \geq \) 12 hours. The %EWL in the treatment subjects was nearly 30%.

**Figure 3.1.** Mean EWL from implant (BMI Method) with standard error at 12 months by categories of average hours of use per day through 12 months

In summary, the results from the EMPOWER trial demonstrated the following:

- There were no deaths or UADEs in the EMPOWER trial. Among all 294 implanted and randomized subjects, only 35 SAEs occurred and only 13 were adjudicated by the CEC as related to either the general surgical procedure, implant/revision procedure, or device. No SAEs related to therapy were observed.
- Mean %EWL from initiation to 12 months was 12.1% treated (n=165) versus 12.0% control (n=88, MetLife method) with all evaluable subjects regardless of compliance (hours of device use).
- %EWL showed strong and statistically significant improvement with greater hours of use per day regardless of the treatment arm:
Clinical Investigational Plan: ReCharge / D01088-000

3.4.5 VBLOC clinical trial design

The VBLOC-DM2 trial is an open label, single-arm, multi-center trial of the Maestro RC2 system conducted at 5 centers outside the United States. This device will be utilized in the ReCharge Clinical Study. All subjects received all implantable components of the RC2 system at the time of implantation. All subjects receive VBLOC Therapy and are followed for five years.

3.4.6 VBLOC-DM2 interim clinical trial results

Twenty eight subjects with type 2 diabetes were enrolled and implanted with RC2 System using the subject’s baseline parameters as control. Seventeen subjects were female and 11 subjects were male. The subject’s mean BMI was 37.0±3.3 kg/m² at screening. Hours of use per day with the RC2 device are approximately 14 hours. Currently, 25 subjects have completed 6 months of follow-up and 25 subjects have completed 12 months of follow-up.

3.4.7 VBLOC-DM2 interim clinical trial safety

There have been no deaths or UADEs among all 28 implanted and randomized subjects. Through 12 months five serious adverse events have occurred. Four events were adjudicated by an independent Clinical Events Committee to not be related to the device or to the procedure to implant the device within the first 12 months. One serious event (pain at neuroregulator site) was adjudicated as definitely related to implant/revision procedure.

3.4.8 VBLOC-DM2 Interim Clinical Trial Efficacy

Efficacy as measured by %EWL was evaluated from implant:

- Mean %EWL from implant to 3 months was 20.8% (n=26, BMI method)
- Mean %EWL from implant to 6 months was 24.4% (n=25, BMI method)
- Mean %EWL from implant to 12 months was 25.3% (n=25, BMI method)
3.4.9  EMPOWER and VBLOC DM-2 Clinical Trial Conclusions

The efficacy results and safety profile of the EMPOWER clinical trial with the RF2 System and VBLOC-DM2 clinical trial with the RC2 System support further clinical development including initiation of a prospective, randomized controlled trial using the Maestro RC2 System in patients with obesity who have not responded to standard weight management using a study design that addresses the confounding EMPOWER variables of device compliance and the unanticipated indication of efficacy of the control group parameters.

3.5  Justification for VBLOC Therapy

EnteroMedics has an extensive understanding of VBLOC therapy with regard to its effect on vagal safety and its effect on the obese patient population.

There have been no reports of therapy-related serious adverse events in any of our current and on-going clinical trials using VBLOC therapy (same therapy used in the treated group of EMPOWER). This population includes 399 patients with over 480 device years of experience. No changes in intra-cardiac conduction (PR interval, QRS duration), ventricular repolarization (QTcF interval) or ventricular arrhythmias were associated with either the treated and control groups from EMPOWER. Heart rate was observed to decrease slightly relative to baseline equally in both groups, a finding consistent with the weight loss observed.

In addition, VBLOC therapy using 5000 Hz has been demonstrated to be safe in the juvenile porcine model in which 71 animals were evaluated. Clinical studies have demonstrated that subjects exposed to 5000 Hz showed a reduction in caloric intake and hunger and early fullness compared to baseline. Greater weight loss was also demonstrated with more extensive vagal inhibition in early clinical feasibility studies.

In the high hours of device use sub-groups, the results of the EMPOWER study suggest greater weight loss in the VBLOC therapy arm compared to the control arm. Clinical studies with the RC device, which minimizes the patient compliance variable, demonstrated weight loss comparable to the high use treated group in EMPOWER and demonstrated that EMPOWER had effective therapy. Improvements in glycemic control and blood pressure in type 2 diabetics with hypertension were also observed in a prospective, open-label, multi-center trial using the Maestro RC2 System to deliver VBLOC therapy.

The EMPOWER study presented the unexpected finding that the control arm appeared to receive some level of active therapy. EnteroMedics has assessed the effect of the control arm parameters on nerve function in the animal model which confirmed an apparent effect. EnteroMedics intends to evaluate this unanticipated therapeutic effect in follow-on scientific and preclinical models.
4.0 Summary and evaluation of prior clinical testing

EnteroMedics Inc. has conducted a series of clinical studies to determine the following:

- The safety profile of the device was excellent based on a low rate of serious adverse events with no therapy-related SAEs and no electrocardiographic findings of concern.
- No difference was observed between the efficacy of the control and treated arms in EMPOWER.
- Greater EWL was observed with greater hours of use in both arms in EMPOWER.
- Confounding variables of hours of device use and unanticipated indication of efficacy of control group parameters were observed in EMPOWER.
- Clinically significant weight loss was observed in subjects who used the device ≥9 hours per day in both arms in EMPOWER.
- The Maestro RC2 system minimizes the confounding variable of hours of use.
- Safety of the Maestro RC2 system is similar to the RF2 system.
- Weight loss achieved in the VBLOC-DM2 trial was comparable to the treated arm ≥9 device use hours per day.
- Improvements in obesity-related co-morbidities was observed in VBLOC-DM2 study.

EnteroMedics concludes that the observations from these studies support the proposed clinical trial.
5.0 Clinical risk benefit analysis

5.1 Potential risks of device implantation and use

Table 5.1 summarizes potential acute and chronic risks associated with:

- Laparoscopic surgical procedures
- Vagal nerve injury
- Vagal blocking therapy and intentional weight loss
Table 5.1. Potential risks of vagal blocking for treatment of obesity

<table>
<thead>
<tr>
<th>Risks</th>
<th>Probability</th>
<th>Severity</th>
<th>Mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intra-operative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>L</td>
<td>4</td>
<td>Implant training; experienced surgical team</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>L</td>
<td>2</td>
<td>Experienced anesthesiology team</td>
</tr>
<tr>
<td>Cardiac (anesthesia related)</td>
<td>L</td>
<td>2</td>
<td>Experienced anesthesiology team</td>
</tr>
<tr>
<td>Bleeding</td>
<td>L</td>
<td>2</td>
<td>Implant training; surgical technique</td>
</tr>
<tr>
<td>Esophageal perforation</td>
<td>L</td>
<td>2</td>
<td>Implant training; surgical technique</td>
</tr>
<tr>
<td>DVT/pulmonary embolus</td>
<td>L</td>
<td>3</td>
<td>Patient selection</td>
</tr>
<tr>
<td>Electrode misplacement</td>
<td>L</td>
<td>3</td>
<td>Training; stimulation and impedance testing</td>
</tr>
<tr>
<td>Electrode malfunction</td>
<td>L</td>
<td>2</td>
<td>Replace electrode</td>
</tr>
<tr>
<td>Vagal nerve injury (mechanical)</td>
<td>L</td>
<td>3</td>
<td>Implant training: atraumatic nerve dissection</td>
</tr>
<tr>
<td><strong>Post-operative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal erosion</td>
<td>L</td>
<td>3</td>
<td>Implant training; atraumatic nerve exposure; clinical follow-up</td>
</tr>
<tr>
<td>Organ entrapment or strangulation</td>
<td>L</td>
<td>3</td>
<td>Experienced surgical team; clinical follow-up</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>L</td>
<td>3</td>
<td>Experienced surgical team; clinical follow-up</td>
</tr>
<tr>
<td>DVT/pulmonary embolism</td>
<td>L</td>
<td>3</td>
<td>Early post-operative ambulation; clinical follow-up</td>
</tr>
<tr>
<td>Vagal nerve injury (mechanical)</td>
<td>L</td>
<td>3</td>
<td>Implant training</td>
</tr>
<tr>
<td>Syncope</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Chest pain</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>L</td>
<td>2</td>
<td>Experienced surgical team; post-op wound care</td>
</tr>
<tr>
<td>Infection, other</td>
<td>L</td>
<td>2</td>
<td>Sterile surgical technique; post-op wound care</td>
</tr>
<tr>
<td>Infection, superficial</td>
<td>M</td>
<td>2</td>
<td>Sterile surgical technique; post-op wound care</td>
</tr>
<tr>
<td>Infection, lead location</td>
<td>L</td>
<td>2</td>
<td>Sterile surgical technique; post-op wound care</td>
</tr>
<tr>
<td>Infection, neuroregulator location</td>
<td>L</td>
<td>2</td>
<td>Sterile surgical technique; post-op wound care</td>
</tr>
<tr>
<td>Inflammation</td>
<td>M</td>
<td>2</td>
<td>Sterile surgical technique; post-op wound care</td>
</tr>
<tr>
<td>Bloating</td>
<td>L</td>
<td>1</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Cramps</td>
<td>L</td>
<td>1</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Edema</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Electrode dislodgement or malfunction</td>
<td>L</td>
<td>2</td>
<td>Design controls; implant training</td>
</tr>
<tr>
<td>Neuroregulator malfunction</td>
<td>L</td>
<td>2</td>
<td>Design controls; implant training; patient training</td>
</tr>
<tr>
<td>Neuroregulator migration or erosion</td>
<td>L</td>
<td>3</td>
<td>Implant training</td>
</tr>
<tr>
<td>Electric shock</td>
<td>L</td>
<td>2</td>
<td>Design controls; Clinical follow-up</td>
</tr>
<tr>
<td>Skin reaction or abrasion to coil</td>
<td>L</td>
<td>2</td>
<td>Alternate attachment methods; clinical follow-up</td>
</tr>
<tr>
<td><strong>Vagal blocking therapy and intentional weight-loss</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Gastroapresis</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Dumping syndrome</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Heartburn/Dyspepsia</td>
<td>M</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>M</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Emesis</td>
<td>M</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Constipation</td>
<td>M</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Eructation</td>
<td>M</td>
<td>1</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Nausea</td>
<td>M</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Energy decrease</td>
<td>L</td>
<td>1</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Alopecia</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Headache</td>
<td>M</td>
<td>1</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>L</td>
<td>1</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Pain</td>
<td>M</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
</tbody>
</table>
### Risks and Mitigation

<table>
<thead>
<tr>
<th>Risks</th>
<th>Probability*</th>
<th>Severity[^]</th>
<th>Mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>L</td>
<td>1</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Appetite changes</td>
<td>L</td>
<td>1</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Flatulence</td>
<td>L</td>
<td>1</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Lightheadedness/Dizziness</td>
<td>L</td>
<td>1</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up; cholecystectomy as needed</td>
</tr>
<tr>
<td>Steatorrhea</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Nerve injury/electrode malfunction</td>
<td>L</td>
<td>2</td>
<td>X-ray and impedance testing</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>L</td>
<td>2</td>
<td>Monitor hemoglobin; supplement as needed</td>
</tr>
<tr>
<td>Calcium deficiency</td>
<td>L</td>
<td>2</td>
<td>Calcium and vitamin D supplementation</td>
</tr>
<tr>
<td>Need for reduction in insulin or other oral hypoglycemic agents</td>
<td>L</td>
<td>2</td>
<td>Monitor diabetic treatment; patient education in self-treatment</td>
</tr>
<tr>
<td>Altered dosage of hypertension medications</td>
<td>L</td>
<td>2</td>
<td>Monitor treatment, clinical follow-up</td>
</tr>
<tr>
<td>Vitamin B deficiencies</td>
<td>L</td>
<td>2</td>
<td>Monitor levels; supplement as needed</td>
</tr>
<tr>
<td>Psychosocial dysfunction</td>
<td>L</td>
<td>2</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Electrode dislodgement or malfunction</td>
<td>L</td>
<td>2</td>
<td>Design controls; implant training</td>
</tr>
<tr>
<td>Neuroregulator malfunction</td>
<td>L</td>
<td>3</td>
<td>Design controls; re-operation</td>
</tr>
<tr>
<td>Possible lead system malfunction or damage resulting in electrical leakage current.</td>
<td>L</td>
<td>2</td>
<td>Design controls; implant training, system monitoring</td>
</tr>
</tbody>
</table>

[^] Probability rated as low (L), medium (M), or high (H);

[^] Severity—1: Negligible (no harm to patient); 2: Marginal (could cause minor injury with short term duration to patient or (e.g., minor burn, cut, etc); 3: Critical (could cause moderate, non-life threatening, injury to patient); 4: Catastrophic (could lead to serious injury or death of the patient).

DVT=deep vein thrombosis

### 5.2 Potential benefits of device use

All eligible subjects can receive up to 60-months long-term monitoring of weight related issues including multiple physical examinations, instruction in the use of a weight management program, and clinical laboratories measurements.

Potentially, subjects will experience some degree of weight loss; however, because determining the amount of weight loss a subject will experience, if any, is the purpose of this investigation, the weight loss benefit is not known.

### 5.3 Device risk analysis and risk assessment

The challenges to health that are posed by obesity constitute a high priority to health care providers and, most importantly, to obese patients and their families. Obesity is a global issue, particularly but not exclusively, in industrialized countries. For example, in the United States, published estimations 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. Two out of every three (66%) adults in the U.S. are either obese (BMI ≥ 30.0 kg/m^2) or overweight (BMI 25.0-29.9). One in twenty people in the U.S. is categorized as extremely obese (BMI ≥ 40). Recent studies document the morbidity and mortality
associated with BMI over 35, as well as the potential benefits accruing to patients with obesity-related co-morbid diseases once significant weight loss is achieved.\textsuperscript{32, 33} There is a well-established association between obesity and clinically significant diseases, e.g., type 2 diabetes, hypertension and osteoarthritis – three leading causes of morbidity and mortality in industrialized countries.\textsuperscript{34} The currently available treatment options do not meet the needs of many obese patients.\textsuperscript{35} Patients who are obese incur 37\% more health care costs than people with normal weight, and spending on obese patients accounted for 27\% of the growth in inflation-adjusted per capita health care spending between 1987 and 2001.\textsuperscript{36}

The consequences of obesity have led to the development of the Maestro System for the treatment of this disease.

- Product development has utilized engineering principles, recognized international standards and testing to optimize therapeutic effects while mitigating the likelihood of adverse events.
- Preclinical mechanism-of-action and preclinical safety studies have documented the physiologic rationale and the safety profile resulting from controllable and reversible intra-abdominal vagal block in preclinical in vivo and ex vivo models.
- Clinical program planning has included close and frequent evaluation of adverse events by an independent panel of physician experts.
- The safety profile of the Maestro RF2 System is excellent.
- The safety profile of the Maestro RC2 system is similar to the RF2 System.

The Clinical Events Committee (CEC) reviewed and adjudicated all serious adverse events observed in the EMPOWER trial. There were no deaths or UADEs in the EMPOWER trial. Among all 294 implanted and randomized subjects, 35 SAEs through 12 months occurred and were adjudicated by the CEC with the following determination of event origin:

- General surgical procedure: 4 (1.4\%)
- Implant/Revision procedure: 5 (1.7\%)
- Device: 4 (1.4\%)
- Therapy algorithm: 0 (0.0\%)
- Pre-existing condition: 17 (5.8\%)
- Not related: 5 (1.7\%)

Note: one additional SAE (CEC-adjudicated as general surgical procedure) in a non-implanted, non-randomized subject is not included in the overall SAE count.

The DSMB reviewed all group 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 treated or control groups from EMPOWER. Heart rate was observed to decrease slightly relative to baseline equally in both groups, a finding consistent with the weight loss observed.
With regard to the Maestro RC2 System used in the VBLOC-DM2 study the following safety profile is reported through the first 12 months:

There have been no deaths or UADEs in the VBLOC-DM2 trial. Among all 28 implanted and randomized subjects. Through 12 months five serious adverse events have occurred. Four events were adjudicated by an independent Clinical Events Committee to not be related to the device or to the procedure to implant the device within the first 12 months. One serious event (pain at neuroregulator site) was adjudicated as definitely related to implant/revision procedure.

The potential benefits of the Maestro System have been evaluated, and the potential risks have been considered and explained in the patient informed consent. Therefore, the clinical evaluation of safety and efficacy of the Maestro RC2 System is appropriate.
6.0 Identification and description of device to be investigated

6.1 Manufacturer and model

The Maestro System is manufactured by EnteroMedics Inc. The components are described in Table 6.1.

Table 6.1. Maestro System Components

<table>
<thead>
<tr>
<th>Implantable Component</th>
<th>Model numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroregulator (RC2)</td>
<td>Model 2002</td>
</tr>
<tr>
<td>Posterior Lead-Marked</td>
<td>Model 2200P-47E</td>
</tr>
<tr>
<td>Anterior Lead-Unmarked</td>
<td>Model 2200A-47E</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>External Components</th>
<th>Model numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile Charger</td>
<td>Model 2402</td>
</tr>
<tr>
<td>Patient Energy Transmit Coil and Cable</td>
<td>Model 2403-60, Model 2403-60A</td>
</tr>
<tr>
<td>Clinician Energy Transmit Coil and Cable</td>
<td>Model 2403-300</td>
</tr>
<tr>
<td>Clinician Programmer</td>
<td>Model 2502</td>
</tr>
<tr>
<td>Programmer Cable</td>
<td>Model 1600</td>
</tr>
<tr>
<td>AC Recharger</td>
<td>Model 1620</td>
</tr>
<tr>
<td>Power Cord (North America)</td>
<td>Model P00173-000</td>
</tr>
<tr>
<td>Power Cord (Australia)</td>
<td>Model P00173-001</td>
</tr>
<tr>
<td>Patient Transmit Coil Belt</td>
<td>Model 1660, Model 1660A</td>
</tr>
<tr>
<td>Torque Wrench</td>
<td>Model 1680</td>
</tr>
</tbody>
</table>

6.2 Intended purpose


Investigational Device To be used by Qualified Investigators only

The Maestro System is under clinical investigation for the treatment of obesity. The system is designed to provide electrical current to block or modulate the anterior and posterior vagal nerves.
6.3 Maestro System general description and use

The Maestro System is intended for clinical investigation in the treatment of obesity. Implantable components of the system include a neuroregulator and two leads. External components of the system include a mobile charger with AC recharger and power cord, transmit coil and cable (patient and clinician), and a clinician programmer used by the study staff. The mobile charger for the implanted neuroregulator is connected via a small, flexible cable to a cutaneous transmit coil that is positioned over the implanted neuroregulator when charging the device. Energy is transferred from the implanted neuroregulator to leads connected to the patient’s anterior and posterior vagus nerves providing blocking or regulation of nerve function.

6.3.1Implantable components

Neuroregulator description
The Model 2002 Maestro Neuroregulator device consists of a hermetic case enclosure surrounded by an external coil that acts as a receiving antenna. See Figure 6.1.

Figure 6.1. Model 2002 neuroregulator & model 2200 leads

The neuroregulator header uses one set screw for connection and fixation of each lead. The neuroregulator contains a 2.6 Ahr Li-ion rechargeable battery, a receiving coil for battery charge, electronics, and connectors for the therapy leads. The neuroregulator receives energy from its internal battery and is recharged transdermally from the transmit coil. If the battery is not charged regularly as recommended it may shut down and an additional visit to the clinic will be required to restart the device. If this condition persists there is a point (~90 days from fully recharged battery) when the battery becomes
unrecoverable and an explant would be required. The neuroregulator should be implanted between 2 and 3 cm below, and approximately parallel to the skin. Implantation 2-3 cm from the skin surface produces optimal telemetry link between the transmit coil and the neuroregulator. The neuroregulator should be placed in the thoracic sidewall or in a location to be determined by the physician.

The neuroregulator is implanted along with a set of therapy leads that apply electrical current to the anterior and posterior trunks of the vagus nerve. Nerve signals are blocked by the application of short, biphasic, charge-balanced electrical pulses at a high pulse rate.

**Lead Description**

Two bipolar leads (Model Numbers 2200P & 2200A) will be implanted as part of the Maestro System therapy. The Model 2200A lead is for the anterior vagal nerve trunk and the Model 2200P lead is for the posterior vagal nerve trunk. The Model 2200 series lead electrode is placed in contact with the appropriate vagal nerve and the lead tongue is sutured to the esophagus and a strain relief is provided by placing suture through the suture wing proximal to the IS-1 connector in the seromuscular layer of the stomach. The connector end of the Model 2200 series leads are IS-1 compatible to allow connection with the neuroregulator.

**6.3.2 External components**

**Mobile Charger description**

The mobile charger is an electronic device worn by the patient externally that connects to the transmit coil and provides information on battery status of the neuroregulator and the mobile charger. The mobile charger recharges the neuroregulator as needed when connected to the cutaneous transmit coil. See figure 6.2.

![Figure 6.2. Model 2402 mobile charger](image)

The neuroregulator and mobile charger are powered by rechargeable, lithium-ion batteries. Patients are required to recharge the neuroregulator battery as indicated by the
display on the mobile charger. The mobile charger recharges the neuroregulator when connected to the transmit coil and positioned over the neuroregulator.

**Transmit Coil description**

The transmit coil is connected to the mobile charger and is worn by the patient externally when recharging the Neuroregulator or determining battery status. See Figure 6.3. There are three different transmit coils available:

- Clinician Transmit Coil – intended for use in the operating room with the Maestro System and is five inches in diameter with a cable 300 cm in length.
- Patient Transmit Coil – intended for patient use with the Maestro System and is five inches in diameter with a cable 60 cm in length. There are two models available; one has a compressed foam overmold (Model 2403-60A) and one does not (Model 2403-60).

**Figure 6.3. Model 2403-60A (Left) and Model 2403-60 (Right) Transmit Coils**

**Clinician Programmer description**

The Model 2502 Maestro System Clinician Programmer (CP) contains software to send and receive information from the neuroregulator. The CP enables the user to configure, monitor and change settings for the neuroregulator as well as the CP itself. The CP provides a graphic user interface to help the user monitor the Maestro System and therapy parameters and schedule.

The users of the CP will primarily be clinicians and EnteroMedics clinical/field staff. Depending on the type of user, the clinician programmer provides varying levels of access to the system.
**Programmer Cable Description**
The Model 1600 Programmer Cable is used to provide connectivity between the Model 2502 Clinician Programmer and the Model 2404 Mobile Charger. The programmer cable is included in the Clinician Programmer Kit.

**AC Recharger Description**
The AC Recharger Model 1620 is a standard power supply used for charging the Mobile Charger battery. The AC Recharger is provided with an appropriate power cord to accommodate the electrical mains connection for the geographic location of the investigational site (Model P00173-000 for US sites and Model P00173-001 for Australian sites).

**Patient Transmit Coil Belt Description**
Patient transmit coil belts are external accessories that may be used to hold the patient transmit coil over the location of the implanted rechargeable neuroregulator during charging of the neuroregulator. The Model 1660 Transmit Coil Belt can be used with the Model 2403-60 Patient Transmit Coil, and the Model 1660A Transmit Coil Belt can be used with the Model 2403-60A Patient Transmit Coil. The Model 1660 Transmit Coil Belt and Model 2403-60 Patient Transmit Coil are included in the Model 2404 Patient Kit. The Model 1660A Transmit Coil Belt and Model 2403-60A Patient Transmit Coil are not included in the Model 2404 Patient Kit but are available as optional accessories to accommodate patient preferences.

**Torque Wrench Description**
The Model 1680 Torque Wrench is a standard surgical wrench provided for use during the implant procedure to tighten set screws that secure the leads to the neuroregulator as described in the implant procedure guide instructions for use. The torque wrench is provided within the sterile neuroregulator package.

### 6.3.3 Description of sham device

The sham neuroregulator for use in the control group is the same device externally as the Model 2002 neuroregulator for use in the treated group. The sham neuroregulator produces typical impedances observed between the nerves using a resistive load included in the neuroregulators’ hermetic enclosure. The neuroregulators’ lead sockets are filled with medical grade silicone adhesive to assure that no electrical currents are delivered by the device. This configuration would provide identical functionality of the typical system for locating the coil over the implant, checking status of the device, charging the neuroregulator, and generating the data provided by the system for review by the clinician. As a result, this configuration would provide adequate blinding of the patient or clinician with no electrical current delivered to the nerves or other tissues.

### 6.3.4 Instructions for use

Please refer to the Technical Manual Instructions for Use for Maestro Obesity Management System and Leads.
6.4 Training

Prior to implanting the Maestro System, each implanting surgeon and clinical coordinator at each investigational site will be fully trained on using the Maestro System including the transmit coil, mobile charger, and programmer and programmer software. Training and documentation of training will be described in a Maestro System Training Plan document.
7.0 Study design and statistical plan

7.1 Study design

This is a randomized, double blind, multi-center trial to evaluate the safety and efficacy of the Maestro system in treating obesity. All subjects will receive an implanted device, and will be randomized in a 2:1 allocation to treatment or control. All subjects will participate in a weight management program, consisting of recommendations regarding diet, exercise, and behavior modification throughout the study. All subjects will remain blinded through the 12-month follow-up visit, after which control subjects who choose to continue in the trial will have the option of a complete Maestro RC2 System implanted and receive therapy.

Type 2 diabetics will be limited to 10% of randomized subjects (no more than 3 subjects per center) and once the enrollment limit is reached, the centers will be notified and type 2 diabetic enrollment will stop.

7.2 Control group description

Subjects randomized to the control group will receive a procedure designed to mimic the procedure used to implant the Maestro RC2 system including:

- Sham surgical procedure, consisting of the same number of incisions the investigator would use with general laparoscopic technique. For control patients, up to five small incisions will be created, through the skin layer only, to simulate placement of 5mm trocars. These incisions may require wound care (e.g., bandages), thus, all subjects (treatment and control) will have the same number of surgical incisions following surgery.
- The control subjects will receive anesthesia, similar to the treatment subjects.
- The control subjects will be implanted with a non-functional neuroregulator which will be placed in a pocket in the same location as the functional neuroregulator. The sham neuroregulator will be designed using resistors that dissipate charge in a manner similar to the active neuroregulator. The battery in the sham device will deplete in the same fashion as the active device and will interact with the programmer in the same way as the active device.

7.3 Objectives

7.3.1 Primary efficacy objective

- The primary efficacy objective is to demonstrate a difference of at least 10% EWL, as measured by the BMI method, at 12 months post-randomization.

- A co-primary efficacy objective is to demonstrate a responder rate in the treatment arm which will achieve the following:
  - at least 55% of subjects in the treated group achieve at least 20% EWL (by BMI) at 12 months and
• at least 45% of the subjects in the treated group achieve at least 25% EWL (by BMI) at 12 months

Note: The co-primary efficacy objective is not statistically based.

Note: Both co-primary efficacy objectives must be met for the trial success to be declared.

7.3.2 Secondary efficacy objective
The secondary efficacy objective is to demonstrate a difference of at least 10% difference in %EWL, as measured by the Met Life method, at 12 months post-randomization.

7.3.3 Primary safety objective
The safety objective of this study is intended to confirm the safety results observed in the EMPOWER study. Safety will be assessed by demonstrating the implant/revision procedure, device and therapy related serious adverse event rate is significantly lower than those associated with adjustable gastric band therapy. This endpoint will be defined as follows:

Device-related Serious Adverse Event Rate =
(Total Number Implant/Revision Procedure, Device, Therapy-Related SAE) / (Number of Patients in the Treatment Group)

The safety objective is as follows:

To demonstrate that the long-term (through 12 months), implant/revision procedure, device and therapy related serious adverse event rate is less than 15%.

7.4 Randomization and blinding
All subjects will be randomized in a 2:1 allocation to the treatment group or control group at the time of device implantation (See below 7.4.1). Randomization for subjects without type 2 diabetes will be stratified according to investigational center. For subjects with type 2 diabetes, there will be no further stratification.

The trial is designed as a double blind trial so that the subject will not know to which treatment group he/she has been randomized. All those responsible for patient follow-up of the subject including coordinators, weight management advisors, and evaluators will also be blinded. Additionally the Sponsors’ management, clinical, engineering, and regulatory groups will be blinded to treatment randomization. Only individuals who have a need to be unblinded, which include the implanting surgeon, the operating room team, and specific sponsor personnel needed to support the safe use of the device, will be unblinded to subject randomization.

Randomization summary:
• Subjects without type 2 diabetes: 2:1 randomization therapy by center
• Subjects with type 2 diabetes: 2:1 randomization therapy across all centers
7.4.1 Randomization

A Sponsor-designated independent statistical center will generate and manage randomizations schedules. Block sizes will be randomized. Sponsor personnel directly involved with the management, conduct, and reporting on the trial will not have access to the randomization assignments. The Data Safety Monitoring Board alone will have access to the randomization assignment upon request.

Randomization of subjects to treatment or control groups will occur at the time of device implantation, and the appropriate device will be implanted and initiated. Regardless of treatment assignment, the programmer will allow for normal programming and testing and will allow for adjusting daily treatment schedules, amplitude settings, ON time and OFF time, Ramp UP time, and impedance measurement parameters. For subjects assigned to the control group the implanted device will output no therapy to the vagal nerves but the coordinators will program the device as usual to maintain blinding.

7.4.2 Blinding

The subject, sponsor (with the exception of specific sponsor personnel needed to support the safe use of the device), and clinical site follow-up staff will be blinded to treatment assignment. Investigators who are responsible for implanting the device and sponsor surgical support staff will not be blinded, due to randomization occurring at the time of device implantation. All subjects will participate in the same study procedures after device implantation for the first 12 months. Subject interaction with other subjects during the first 12 months of the study will also be minimized.

Under normal operation, the system supports the blinding in the following ways:

- The neuroregulator battery will deplete at a similar rate for both the sham and active devices requiring the same device recharging schedule. Therefore, patients in both groups will recharge the device using the patient transmit coil and mobile charger.
- The neuroregulator and sham device will be programmed using the same Maestro System Clinician Programmer (CP) following the same procedures and schedule for therapy adjustment. The sham device will transmit no therapy to the vagal nerve, however, this is not expected to be noticed by the subjects.

At the 1 week, 6 month and 12 month follow-up visits or if a subject exits the trial before the 12 month visit, each subject will be asked to which treatment group he/she believes they were assigned or whether they “don’t know” and the response will be recorded on the appropriate case report form. Control subjects who choose to continue in the trial after twelve months will have the option to have a complete Maestro RC2 System implanted and to receive VBLOC therapy.

**Unblinding**

The treatment assignment for a subject will be unblinded only in the following circumstances:

1) In the event of medical emergency where it is medically necessary to know if the subject was or was not receiving therapy or have leads implanted.
2) After a majority of study subjects have completed their 12-month visits, the site and study subjects will be unblinded as to treatment assignment. No subject will be unblinded prior to their 12-month visit.

7.5 Efficacy statistical evaluation

7.5.1 Primary efficacy objective

The primary efficacy objective is to demonstrate at least a 10% difference in %EWL, (BMI method), at 12 months post-randomization. The average %EWL at 12 months post-randomization will be compared across treatment groups to test for a statistical difference greater than 10%.

7.5.1.1. Endpoint

The primary endpoint is the %EWL at 12 months post-randomization.

7.5.1.2. Parameter of interest

The parameter of interest is the average %EWL (BMI method) at 12 months post-randomization for each group.

7.5.1.3. Experimental design

This is a randomized, parallel group, super-superiority design evaluating the effect of treatment 12 months post-randomization as compared to a control group.

7.5.1.4. Hypotheses

\[
H_0: \mu_{\text{TRT}} \leq \mu_{\text{CTL}} + \Delta \\
H_a: \mu_{\text{TRT}} > \mu_{\text{CTL}} + \Delta
\]

where \( \mu_{\text{TRT}} \) is the average %EWL (BMI method) from randomization for those assigned to the treatment group, \( \mu_{\text{CTL}} \) is the average %EWL from randomization for those assigned to the control group and \( \Delta \) is the pre-specified superiority margin of 10% EWL.

7.5.1.5. Sample size estimation

Sample size is calculated using SAS V9.2 software (Proc Power) to compare two means in a one-sided Student’s t-test. The minimum required sample size was calculated under the following assumptions:

- Significance level = 2.5%
- Power = 85%
- Expected difference (treatment – control) in %EWL = 20%
- Expected standard deviation = 22%
- Superiority margin = 10%
- 2:1 randomization allocation

Under the assumptions outlined above, the estimated minimum required sample size is 198 subjects (132 treatment, 66 control).
7.5.1.6. Data analysis
The primary analysis will be conducted according to the principles of intent-to-treat. If any subject does not have endpoint data available at 12 months, the “last value carried forward” (LVCF) imputation method will be applied to the missing 12 month data points. Sensitivity and supportive analyses will include a ‘completer’ analysis (excluding subjects with missing endpoint data) and a longitudinal, repeated measures mixed model regression analysis. Further sensitivity analysis will include a ‘worst-case’ analysis and a ‘tipping point’ analysis (e.g., determine how many "favorable" missing values would be needed to tip the observed result in favor of control, statistically).

Assessment of baseline characteristics by treatment group will be conducted. If differences exist, those variables will be assessed for effect on the treatment comparison. If the variable is associated with a significant effect on the primary endpoint, or if an interaction exists at the 0.10 significance level, the primary analysis will include that variable as a covariate adjustment.

7.5.2 Secondary efficacy objective
The following secondary objective will be assessed. In order to maintain an overall 5% type I error rate, Hochberg’s method will be used to control type I error. This hypothesis test will only be conducted if the primary efficacy objective is met.

7.5.3 Secondary efficacy objective
The secondary efficacy objective is to demonstrate at least a 10% difference in %EWL (Met Life method), at 12 months post-randomization. The average %EWL at 12 months post-randomization will be compared across groups to test for a statistical difference of at least 10%.

7.5.3.1. Endpoint
The endpoint is the %EWL (Met Life method), at 12 months post-randomization.

7.5.3.2. Parameter of interest
The parameter of interest is the average %EWL (Met Life method) at 12 months post-randomization for each group.

7.5.3.3. Experimental design
This is a randomized, parallel group, super-superiority design evaluating the effect of VBLOC Therapy 12 months post-randomization for the treatment and control groups. The primary analysis will be conducted according to the principles of intent-to-treat. If any subject does not have endpoint data available at 12 months, the “last value carried forward” (LVCF) imputation method will be applied to the missing 12 month data points. Sensitivity and supportive analyses will include a ‘completer’ analysis (excluding subjects with missing endpoint data) and a longitudinal, repeated measures mixed model regression analysis.
7.5.3.4. Hypotheses

\[ H_0: \mu_{\text{TRT}} \leq \mu_{\text{CTL}} + \Delta \]
\[ H_1: \mu_{\text{TRT}} > \mu_{\text{CTL}} + \Delta \]

where \( \mu_{\text{TRT}} \) is the average \%EWL (Met Life method) at 12 months post-randomization for those assigned to the treatment group, \( \mu_{\text{CTL}} \) is the average \%EWL (Met Life method) at 12 months post-randomization for those assigned to control, and \( \Delta \) is the pre-specified superiority margin of 10%.

7.5.3.5. Power estimation

Power is calculated using SAS V9.2 software (Proc Power) to compare two means in a one-sided Student’s t-test. The minimum required sample size was calculated under the following assumptions:

- Significance level = 2.5%
- Expected difference (treatment – control) in \% EWL = 20%
- Expected standard deviation = 22%
- Superiority margin = 10%
- 2:1 randomization allocation
- Total evaluable sample size = 198 (132 treatment and 66 control subjects)

Under the assumptions outlined above, 198 subjects (132 treatment, 66 control) provide approximately 85% power.

7.6 Safety evaluation

Safety will be evaluated via one primary safety objective. For this endpoint, an objective performance goal (OPG) has been established based on reported results from IFUs of FDA approved gastric adjustable band devices. The objective must be met in order to satisfy safety requirements.

7.6.1 Primary safety objective

To demonstrate that the implant/revision procedure, device and therapy related serious adverse event rate through 12 months is less than 15%.

7.6.1.1. Parameter of interest

The parameter of interest is the proportion of subjects in the treatment group that experience an implant/revision procedure, device and therapy related serious adverse event rate through 12 months post-implant. Serious adverse events are defined in Section 9.10 of this protocol. All SAEs included in this parameter will be reviewed by an independent clinical events committee, and classified according to severity and relatedness.

7.6.1.2. Experimental design

This is a single-arm assessment of all long-term, device-related complications. All subjects randomized to the treatment group will be included in the evaluation.
7.6.1.3. Hypothesis

\[ H_0: \pi_{trt} \geq OPG \]
\[ H_0: \pi_{trt} < OPG, \]

where \( \pi_{trt} \) is the proportion of subjects experiencing a long-term, device related complication and OPG is the pre-specified objective performance goal of 15%.

In order to determine an appropriate objective performance goal (OPG), the labeling for both FDA-approved adjustable gastric band devices was reviewed. As indicated in the labeling, there were 69 device related SAEs for the REALIZE band and an estimated 115 device related SAEs for the LAP-BAND within the first three years.

The following table summarizes the SAE rate observed at three years for both the REALIZE and LAP-BAND devices.

<table>
<thead>
<tr>
<th></th>
<th>Realize (n=276)</th>
<th>LAP-BAND (n=299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device related SAE Rate (# of events/# of patients)</td>
<td>25.0% (69/276)</td>
<td>38.5% (115/299)</td>
</tr>
<tr>
<td>Follow-up Time Frame</td>
<td>3 Year</td>
<td>3 year</td>
</tr>
</tbody>
</table>

The one year device related SAE rates were not available for either the REALIZE band or the LAP-BAND. Consequently, it was assumed that the majority of the device related SAEs occur within the first year of the procedure. The LAP-BAND study was the first investigation of an adjustable gastric band and improvements in surgical technique have been made over the years. Therefore, we assumed that a more current SAE rate would be lower. With these assumptions, the one year objective performance goal (OPG) will be 15%.

7.6.1.4. Power estimation

Estimated power for this objective was calculated using SAS V9.2 software, under a one-sample exact binomial test. The estimated power was calculated under the following assumptions:

- Significance level = 2.5%
- Minimum sample size of 132 subjects
- OPG = 15%
- Underlying implant/revision procedure, device and therapy related serious adverse event rate = 6.75%

Under the assumptions outlined above, approximately 132 subjects will provide greater than 80% power to evaluate this objective.
7.7  **Size and duration of trial**
A minimum of 198 randomized, evaluable subjects is required to sufficiently power (≥ 85%) the primary efficacy objective. This sample size provides sufficient power to assess the primary safety objective and secondary efficacy objectives. Approximately 234 obese subjects at up to 12 centers will be randomized, allowing for approximately 15% attrition in the first 12 months of follow-up.

Minimum follow-up on each subject will be 12 months, except in the case of death, losses to follow-up, subject withdrawal, or other censoring events.

7.8  **Supportive analysis**
The following analyses will be performed and the results will be reported to provide supportive evidence of the safety and efficacy of the Maestro RC2 System. No formal tests of hypotheses will be performed for these assessments. The longitudinal analysis plan includes long-term summaries of sustained weight loss as well as repeated measures, mixed model regression analyses through 12 months post-randomization and through four years of additional follow-up.

1. Summarize the percentage of total body weight loss for each treatment group.
2. Summarize changes in HbA1c for each treatment group.
3. Summarize changes in each of the subject questionnaires collected for each treatment group.
4. Summarize changes in Body Mass Index (BMI) for each treatment group.
5. Summarize changes in waist circumference and waist-hip ratio for each treatment group.
6. Summarize changes in systolic blood pressure, diastolic blood pressure and mean arterial pressure for each treatment group.
7. Summarize changes in gluco-regulation and lipoprotein profile for each treatment group.
8. Summarize subject’s participation in weight management sessions and other dietary information.
9. Summarize findings from ECG testing.

7.9  **Strengths and limitations**

**Strengths**
Major strengths of this study include:

- Randomized, double blind, multicenter, sham-controlled trial
- Primary endpoint assessed at 12 months, with follow-up extended through 5 years
- All subjects will have the opportunity to receive active treatment after 12 months and will be followed for an additional 4 years.
Limitations
The potential limitations in the experimental design include:

- Subject compliance with using the system as directed, i.e., with requirements to regularly recharge the battery
- Subjects assigned to the control group will need to undergo an additional surgery to receive therapy
- After 1 year, the control group will have the opportunity to receive therapy which prevents further comparisons between the treated group and the control group.
8.0 Study population

8.1 Inclusion criteria

Candidates for this trial must meet all of the following criteria:

1. Informed consent

2. Body mass index (BMI) \( \geq 40 \text{ kg/m}^2 \) to 45 kg/m\(^2\) or BMI \( \geq 35 \text{ kg/m}^2 \) 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 criteria #5 (limited to 10\% of randomized subjects)
   - Hypertension as defined by systolic pressure \( \geq 140 \text{ mmHg} \) and/or diastolic pressure \( \geq 90 \text{ mmHg} \)
     - treated or untreated with systolic \( \geq 140 \text{ mmHg} \) and/or diastolic \( \geq 90 \text{ mmHg} \)
     - treated with systolic \( <140 \text{ mmHg} \) and/or diastolic \( <90 \text{ mmHg} \)
   - Dyslipidemia as defined by total cholesterol \( \geq 200 \text{ or LDL} \geq 130 \)
     - treated or untreated with total cholesterol \( \geq 200 \text{ or LDL} \geq 130 \)
     - treated with total cholesterol \( <200 \text{ or LDL} <130 \)
   - Sleep apnea syndrome (confirmed by overnight p02 studies)
   - Obesity-related cardiomyopathy

3. Females or males

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

4. 18-65 years of age inclusive

5. Type 2 diabetes mellitus subjects with:
   - Glycosylated hemoglobin (HbA\(_{1c}\)) 7.0-10 \% inclusive at screening visit
     (Undiagnosed subjects that are found to have a HbA\(_{1c}\) 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 of proliferative retinopathy
   - No history peripheral neuropathy
   - No history of autonomic neuropathy
   - No history of coronary artery disease, with or without angina pectoris
   - No history of 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

8.2 Exclusion criteria
Candidates will be excluded from the trial if any of the following conditions apply:

1. Concurrent chronic pancreatic disease
2. History of Crohn’s disease and/or ulcerative colitis
3. History of bariatric surgery, fundoplication, gastric resection or major upper-abdominal surgery (acceptable surgeries include cholecystectomy, hysterectomy)
4. History of pulmonary embolism or blood coagulation disorders
5. Clinically significant hiatal hernias (>5cm) known from subject’s medical record or determined by barium swallow (upper GI x-ray) or upper endoscopy per PI discretion prior to implant.
6. Current cirrhosis, portal hypertension and/or esophageal varices
7. Intra-operative exclusion: hiatal hernia requiring surgical repair or extensive dissection at esophagogastric junction at time of surgery
8. 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
9. Smoking cessation within the prior six months
10. Known genetic cause of obesity (e.g., Prader-Willi Syndrome)
11. Weight loss of more than 10% of body weight in the previous 12 months
12. 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 [see exclusion criterion #24]
13. Current type 1 diabetes mellitus (DM)
14. Current or recent history (within 12 months) of ongoing bulimia
15. Current alterations in treatment for thyroid disorders (stable treatment regimen for prior three months acceptable)
16. Current alterations in treatment for epilepsy (stable treatment regimen for prior six months acceptable)
17. Current treatment for peptic ulcer disease (previous history acceptable)
18. Chronic treatment (more than 4 weeks of daily use) with narcotic analgesic drug regimens (treatment with non-steroidal anti-inflammatory drugs acceptable)
19. Current alterations in treatment regimens of anti-cholinergic drugs, including tricyclic antidepressants (stable treatment regimen for prior six months acceptable)
20. 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

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

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

23. 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 \( \geq 29 \) will be considered to indicate severe depression.

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

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

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

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

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

8.3 Point of enrollment
Subjects will be considered enrolled in the study after they have signed the informed consent, have met all inclusion/exclusion criteria and randomized. Subjects who undergo surgery but who are not subsequently implanted with the device will be followed as needed to assess any adverse events and exit the trial.

8.4 Randomization to treatment and subject replacement
Subjects who discontinue the trial after being randomized at the implant visit will not be replaced.

8.5 Subject status at twelve months and final trial status
Twelve month status
Each randomized subject’s status at twelve months will be classified into one of the following:

- Withdrew prior to 12 months
• Active at 12 months
• Withdrew at 12 months
• Active at 12 months but did not complete 12 month visit

Final Status
Each subject’s final status in the trial will be classified into one of the following categories:

1.Exited trial at device implant/randomization
2.Exited trial after randomization to treatment

Additionally, the investigator will record one of the following as the primary reason for trial exit on the appropriate case report form:

• Did not meet inclusion/exclusion criteria
• Failure to implant
• Adverse event
• Death
• Lack of compliance with therapy / weight management program
• Lost to follow-up
• Subject decision not to continue in study, specify____________________________
• Investigator decision to withdraw subject from study, specify____________________________
• Other, specify____________________________
9.0 Variables to be measured and methods for assessing, recording, and analyzing variables

9.1 Body height, body weight, body mass index, excess body weight, and excess body weight loss (EWL)

To determine eligibility for the trial and to assess trial objectives, subjects will have body height, and body weight measured at time points identified in Table 2.1 and Table 2.2. Excess body weight will be used to calculate subjects’ excess body weight loss (EWL) over the course of the trial.

**Body height**
Body height will be measured with the subject’s shoes off to the nearest 0.01 meter (m) using the clinic’s routinely used stadiometer. The subject’s height will be measured once at the screening visit.

**Body weight**
Body weight will be measured with the subject only in underwear and in hospital gowns to the nearest 0.1 kilogram (kg) using electronic scales. If body weight is unable to be measured in this fashion, it will be measured by a method routinely used by sites. The subject will be weighed using the same methodology and instrument throughout the trial (e.g., a subject weighed on an electronic scale at screening will be weighed on the same electronic scale at all subsequent trial visits).

**Body mass index (BMI)**
The BMI will be calculated at screening to determine if subjects meet the BMI inclusion criterion. Body mass index is calculated by dividing body weight (kg) by body height (m) squared (BMI=kg/m²).

Leading health organizations including World Health Organization, Centers for Disease Control and Prevention, National Institutes of Health, and American Society for Bariatric Surgery, and most recently, The Obesity Society, have all adopted and recommend the use of Body Mass Index (BMI) as the standard method to define categories of body weight. The following classifications have been widely accepted and are the favored categories of obesity classification and an estimate of relative risk of morbidity (such as hypertension, high blood cholesterol, type 2 diabetes, coronary heart disease, and other diseases) and mortality.

<table>
<thead>
<tr>
<th>Obesity Class</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
</tr>
<tr>
<td>Obesity Class I</td>
<td>30.0 – 34.9</td>
</tr>
<tr>
<td>Obesity Class II</td>
<td>35.0 – 39.9</td>
</tr>
<tr>
<td>Obesity Class III</td>
<td>≥ 40</td>
</tr>
</tbody>
</table>
**Excess body weight**

Excess body weight (defined as baseline weight minus ideal body weight) will be determined and reported by the Sponsor.

For the primary efficacy objective and supportive analysis ideal weight will be calculated by assigning ideal body weight with a weight corresponding to a BMI of 25\(^4\) for a person of a given height. For example, for a person who is 157 centimeters tall, the value of 61.6 kilograms will be used as ideal body weight as it corresponds to a BMI of 25, using the equation of weight = 25 x height\(^2\). This is referred to as the BMI method.

For the secondary efficacy endpoint ideal body weight will be calculated based on the Metropolitan Height and Weight Tables\(^4\) (see Appendix A: Metropolitan height and weight tables for men and women on metric basis according to body frame size, ages 25-59 in indoor clothing). This will be done by assigning all subjects to a medium frame size and using the respective upper weight for the range for their gender and height. Height and weights will be adjusted for shoes and clothing as noted in the Metropolitan Height and Weight Tables. This is referred to as the MetLife method.

**Excess body weight loss (EWL)**

Excess body weight loss (EWL) is expressed as a percentage. %EWL is calculated by dividing weight loss by excess body weight and multiplying by 100 [%EWL = (weight loss/excess body weight) x100].

9.2 **Waist and hip circumference**

All waist and hip circumference measurements will be completed at times as noted in Table 2.1 and Table 2.2. All measurements will be made using calibrated Gulick II tape measures supplied by the sponsor for accurate circumference measurements. To perform a measurement, pull the appropriate amount of tape out of the housing. Wrap the tape around the waist or hip. Align the tape’s zero line alongside the tape graduations. Pull the end with the tension mechanism until you see one red ball and the edge of the silver disk, this is the calibration point. Do not pull so hard that two beads with the silver disk between them start to disappear into the end of the tension device; that is too much force.

9.2.1 **Waist circumference**

Waist circumference will be measured at the times noted in Table 2.1 and Table 2.2, and it will be measured in the following manner. First, to define the level at which waist circumference is to be measured; a bony landmark is located and marked. The subject stands and the examiner, positioned at the right of the subject, palpates the upper hip bone to locate the right iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin (see Figure 9.1 below). The measurement is made at a normal minimal respiration. (NHANES III Protocol - third National Health and Nutrition Examination anthropometric procedures).
Figure 9.1. Measuring tape position for waist circumference

9.2.2 Hip Circumference
Hip circumference will be measured at times noted in Table 2.1 and Table 2.2, and it will be measured in the following manner. The tape is placed at the maximum extension of the buttocks. The plane of the tape is parallel to the floor and the tape is snug, but not tight (NHANES III Protocol - third National Health and Nutrition Examination anthropometric procedures).

9.3 Medical history and physical examination
All subjects will have a complete medical history and physical examination at screening to help determine eligibility for the trial. At subsequent trial visits, subjects may have interim physical examinations at the discretion of study staff. All findings will be recorded on the appropriate case report form.

Complete medical history
A complete medical history will be collected at the screening visit. Complete medical history will include history of disease, current symptoms, known drug allergies, and current medication use, assessment of alcohol / drug abuse, allergy, cardiovascular, dermatologic, endocrine, gastrointestinal, hematologic, musculoskeletal, neurologic, psychiatric, respiratory, and surgery. As part of the medical background, history specific to obesity and tobacco use will also be collected.

Initial physical examination
The complete physical examination will include assessment of abdomen, lymph nodes, extremities, head and neck (including thyroid), heart, lungs, musculoskeletal, neurologic (reflexes), skin, and other (describe).
Interim physical examination (as needed)

The brief physical examination will consist of an assessment of the abdomen, heart, lungs, and other (describe). If the subject states that changes have occurred related to systems not assessed, then these systems should also be examined.

The physical examination data to be recorded on the case report form will include (1) the status of finding (e.g., normal, abnormal, not done), and (2) a description of any abnormalities. At subsequent physical examinations, only findings that have changed in status from the previous examinations (e.g., findings that were normal and are now abnormal, or findings that were abnormal and are now normal) will be recorded on the appropriate case report form.

9.4 Medication use assessment

Investigators will record all medications the subject is currently using, excluding all pre-, peri- and post-operative medications given as part of the implant procedure, on the appropriate case report form (CRF). The CRF will ask for the following information for each medication taken by the subject:

- Class/indication of medication
- Name of medication
- Reason for change
- Total daily dose
- Start date and date of any changes to dosage

9.5 Electrocardiograms (ECGs)

To assess cardiac rate and rhythm, a 12-lead electrocardiogram (ECG) will be completed at the time points described in Table 2.1 and sent to an ECG core lab for evaluation. During visits after randomization the ECG should be performed with therapy ON. At minimum, the core lab will evaluate the heart rate, heart rhythm, PR interval, QRS duration, QT interval and QTc interval. The ECG core lab will provide the Investigator with instructions on collecting and transmitting ECG recordings.

9.6 Vital signs

Vital signs consist of sitting pulse, sitting blood pressure, and body temperature. These will be measured after subjects have been seated for at least five minutes at times noted in Table 2.1 and Table 2.2. Values will be recorded on the appropriate case report form.

Pulse will be determined while the subject is seated by palpation of the radial pulse for a period of 30 seconds and then multiplied by two.

Blood pressure will be measured while the subject is seated using a generally accepted cuff method as described below.

The blood pressure measurements at the visits noted below will be measured and recorded three times each with a 5 minute interval between measurements. The Sponsor will use the mean of the three measures as the final result.
1. **Screen**
2. **Implant**
3. **Months:** 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60

**Method for collecting blood pressure using standard sphygmomanometer**:

1. Patient should be seated for at least 5 minutes with back supported, arm supported at heart level, elbow slightly flexed, and legs uncrossed.
2. Select appropriate size cuff. The "ideal" cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1). The same size cuff should be used throughout the study unless the arm circumference changes to another size.
   a. For arm circumference of 27 to 34 cm, use "adult" size: 16x30 cm
   b. For arm circumference of 35 to 44 cm, use "large adult" size: 16x36 cm
3. Palpate the brachial artery in the antecubital fossa and place the midline of the bladder of the cuff (commonly marked on the cuff by the manufacturer) so that it is over the arterial pulsation over the patient's bare upper arm. The patient’s sleeve should not be rolled up such that it has a tourniquet effect above the blood pressure cuff. The lower end of the cuff should be 2 to 3 cm above the antecubital fossa to allow room for placement of the stethoscope.
4. Place stethoscope bell below the antecubital space over brachial artery.
5. Inflate cuff pressure to at least 30 mm Hg above the point at which the radial pulse disappears.
6. Slowly release pressure at rate equal to 2 to 3 mm Hg/sec noting first Korotkoff sound (systolic BP).
7. Continue releasing pressure, noting when sound disappears (5th phase diastolic BP).
8. Record values to the nearest 2 mm Hg when the first and last sounds are observed.

Body temperature will be measured orally or by a method routinely used by sites as long as the method used is the same for all subjects at a site.

**9.7 Clinical laboratory tests**

During screening and throughout the course of the trial, blood will be collected for screening and safety assessments at times noted in Table 2.1 and Table 2.2. All blood samples should be drawn with the subject fasting for at least 8 hours. All attempts should be made to ensure the subjects fasted overnight; however, the actual fasting duration will be collected and recorded on the appropriate form.

Abnormal laboratory values must be assessed for clinical significance by the investigator or designated physician. If the result is outside the normal range, the subject may continue in the trial if the investigator judges that the abnormal value(s) will not jeopardize the subject’s health and successful completion of the trial. The development of a clinically relevant deterioration in a laboratory variable will constitute an adverse event, which is to be recorded on the appropriate case report form.

The clinical laboratory assessments consist of the following:
Chemistry
According to central laboratory requirements an appropriate sample of blood (approximately 20 mL) will be drawn and collected into a serum separator tube in order to determine: serum sodium, potassium, chloride, bicarbonate (carbon dioxide), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, blood urea nitrogen, creatinine, total bilirubin, glycosylated hemoglobin (HbA1c), blood glucose, serum triglycerides, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL-calculated), C-reactive protein, folic acid, vitamin B12, total iron-binding capacity (TIBC), iron, calcium, phosphate, magnesium, vitamin D.

Hematology
According to central laboratory requirements an appropriate sample of blood (approximately 5 mL) will be collected to determine: red blood cells (RBC), hemoglobin, hematocrit, white blood cells (WBC), and platelet count.

Urine pregnancy test
For all female subjects of child-bearing potential, a urine pregnancy test will be completed at the Screening visit and at the time of implant if the previous test was done more than 14 days prior.

Estimate of blood volume drawn
During the screening period and throughout the course of the 60-month trial, the estimated total blood volume to be drawn will be 250 mL for each subject.

Central Laboratory
A central clinical laboratory will provide all sample collection and shipping materials as well as perform all the assays for the tests described. They will also provide an investigators’ manual of instructions and methodology for sample collection, storage, and shipment.

9.8 Subject questionnaires
At four times the first year and eight times in the next four years of follow-up, the subject will complete questionnaires listed below at the time points noted in Table 2.1 and Table 2.2. The questionnaires described below will be provided for the subjects to complete.

9.8.1 Hunger and appetite questionnaire
At time points noted in Table 2.1 and Table 2.2, subjects will complete a hunger and appetite questionnaire. This questionnaire uses visual analogue scales (VAS) and questions to assess changes in appetite and hunger. It is usually completed within less than 2 minutes.

9.8.2 Three-Factor Eating Questionnaire (TFEQ)
At time points noted in Table 2.1 and Table 2.2 subjects will complete the Three-Factor Eating questionnaire (TFEQ)\(^46\). This self-report questionnaire is used to measure the psychological constructs of eating on three subscales that assess hunger, disinhibition,
and cognitive restraint. There are 36 true/false questions and 36 multiple choice questions. It is usually completed within approximately 10-15 minutes.

### 9.8.3 Impact of Weight on Quality of Life Questionnaire-Lite (IWQOL-Lite)

The Impact of Weight on Quality of Life Questionnaire-Lite (IWQOL-Lite) has 36 questions that measure 5 areas or domains (physical function, self-esteem, sexual life, public distress, and work). Publications of psychometric properties indicate good test-retest reliability and internal consistency and also indicate that IWQOL-Lite demonstrates responsiveness to weight loss. It is usually completed within approximately 10 minutes.

### 9.8.4 Beck Depression Inventory (BDI®-II)

Assessment of depression as rated by the subject using the Beck Depression Inventory-II (BDI-II) 21 questions has good psychometric properties (test-retest reliability, internal consistency and validity are well established), and it has minimal inclusion of items that would be biased by obesity. It is usually completed within approximately 5 minutes.

### 9.9 Psychological Assessment

All subjects will receive a psychological assessment during the screening visit by a licensed psychologist/psychiatrist or designee preferably with experience in the bariatric population.

### 9.10 Implant procedure information

The following device and surgical procedure information at time of implant will be collected on the appropriate source document at the time of the procedure:

- Device information
- Neuroregulator placement information

Video and/or photographic record of implant (neuroregulator and, as applicable, lead placement) will be made and provided to the Sponsor.

### 9.11 Adverse events (AEs) and unanticipated adverse device effects (UADEs)

The safety assessment will include recording of adverse events (AEs), including unanticipated adverse device effects (UADEs) that occur during the trial. AEs will be followed until they normalize by the Investigator or designee. All UADEs shall be reported to the sponsor within 72 hours of learning of the event. Additionally, the reviewing institutional review board should be notified of all UADEs as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

All adverse events must be captured without judgment and reported on the appropriate case report form. Reporting an AE does not necessarily reflect a conclusion by the investigator or sponsor that the event is causally related to the device. All AE reports must contain the date the adverse event occurred, a brief description of the event, duration of event, the severity, the treatment required, the outcome, and the relationship to the device.
The investigator must report all serious adverse events (SAEs) and unanticipated adverse
device effects to the sponsor within 72 hours of learning of the event. Reporting SAEs to
the institutional review board is not required per FDA regulations, but reporting the SAE
may be required as determined by each institutional review board.

UADEs, serious adverse events, and additional adverse event types identified in the
DSMB Charter will be reviewed by an independent event adjudication committee.

Definitions

Adverse event (AE): Any untoward medical occurrence in a subject
Note: This definition does not imply that there is a relationship between the adverse event
and the device under investigation.

Serious adverse event (SAE): An adverse event that:

1. Leads to death
2. Leads to serious deterioration in the health of the subject that
   a. results in a life-threatening illness or injury
   b. results in a permanent impairment of body structure or body function
   c. requires in-patient hospitalization or prolongation of existing
      hospitalization
   d. results in medical or surgical intervention to prevent permanent
      impairment to body structure or a body function.

Note 1: In-patient hospitalization is defined and determined by the policies of
each institution but does not include emergency room care and/or treatment
observation area visits.

Note 2: System revisions and/or system removals that are required because of an
adverse event should be considered a SAE if it meets the definition above.
System revisions and/or removals that occur for other reasons, such as the
subject’s choice, or battery diminishment may not meet the definition of SAE.

Unanticipated adverse device effect (UADE): Any serious adverse effect on health or
safety or any life-threatening problem or death caused by, or associated with, a device, if
that effect, problem, or death was not previously identified in nature, severity, or degree
of incidence in the investigational plan or application (including a supplementary plan or
application), or any other unanticipated serious problem associated with a device that
relates to the rights, safety, or welfare of subjects.

Note 1: This definition includes any event resulting from insufficiencies or inadequacies
in the instructions for use or the development of the device.

9.12 Technical observations

A technical observation is defined as a failure or malfunction of the device or system
(e.g., any component is faulty either prior to or after implant). Technical observations
associated with clinical events will be reported on the appropriate case report form.
Clinical events not associated with device malfunction or failure are not considered technical observations but will be reported on the appropriate case report form.
10.0  Study conduct

10.1  Weight management

The ReCharge behavioral weight loss program was developed in collaboration with Department of Epidemiology at the University of Minnesota’s School of Public Health and will be used to assist participants in the clinical trial with their weight control. This is the same program as was used in the previous EMPOWER study. All subjects will participate in the program regardless of randomization group. The program will provide educational material for subjects to keep track of their diet and exercise and make modifications to reach their study goals. In the first year of the program, all subjects are taught the same basic information about weight loss and physical activity and are given the opportunity to practice related behavioral skills both during educational sessions and at home. Modifications to their current diet and exercise plan will be taught by a trained adviser through seventeen individual sessions during the first year along with the regularly scheduled trial visits. Prior to the implant, weeks one through four and once per month during the first year of the study the subject will be provided and required to complete a 7 day diet and exercise diary. Following the first year, group sessions will be scheduled for the duration of the study. During initial sessions, subjects will learn a new topic and discuss the progress of their weight control. Self-monitoring, goal setting, and home activities are included in follow up sessions to reinforce the participant's sense of personal responsibility for the success of the education. The curriculum for the first two years is attached in Appendix B: Weight management – Year One outline and Year Two outline.

Advisers will be selected at each approved clinical site with a preferred background in exercise physiology, nutrition or behavior modification. The role of the Adviser is to guide and educate the participant in the process of self-management. A manual of procedures will be provided for all advisers to follow. The purpose of the manual is to provide information on the behavioral weight loss goals, a description of underlying key principles, detailed instructions for leading each session, and strategies for responding to participant concerns. Advisers will be blinded to randomization assignment through 12 months.

10.1.1  Type and frequency of contact during Year One

Subjects must cover the elements of the curriculum in a minimum 17 individual face-to-face sessions in the first 12 months after initiation to complete the year one behavioral weight loss instruction. The first session is 45 minutes long, sessions 2-4 are 30 minutes long and the remaining 13 sessions are 15 minutes long.

10.1.2  Type and frequency of contact during Years Two through Five

The weight management adviser will provide the following individual and group sessions. All sessions completed will be recorded on the case report form. Note that control subjects who receive an active device will follow the year one schedule for the first 12 months after implantation.
10.1.2.1. Individual sessions
During required study visits weight management advisers may meet with the study coordinator and complete the visit together or meet individually. During the visit, a recommended 15 minutes and a maximum of 30 minutes will be spent with the subject reviewing their caloric intake, activity level, and enthusiasm in the study. Materials from the first year may be reviewed as necessary.

10.1.2.2. Group sessions
Beginning after subjects are unblinded at 12 months, group sessions will be held every month. Subjects should be encouraged to attend as many group sessions as they can, and they are required to attend a minimum of 4 group sessions within the year. Year Two sessions are numbered 18-28. Years three through five topic suggestions will be provided to each center.

Each session will last approximately one hour. It may be necessary to have multiple group sessions to accommodate all subjects’ schedules (i.e., morning and evening sessions). It is recommended that sessions are limited to 12-15 subjects.

10.1.3 Food diaries
A food diary is provided as part of the Weight Management Program; however, if a subject wants to use an alternate method to record food diaries, either paper diaries or electronic forms found in computer programs or on the internet, that is acceptable and can be encouraged as long as the completed food diaries can be shared with the Weight Management Adviser at the required session.

10.2 VBLOC Therapy delivered via the Maestro System

10.2.1 Intra-abdominal anterior and posterior vagal nerve trunk block
The Maestro RC2 System is designed to deliver therapeutic electronic algorithms in order to reversibly, controllably, and intermittently block the intra-abdominal anterior and posterior vagal nerve trunks.

10.2.2 Definition of terms for treatment
Blocking: a partial or complete inhibition of the propagation of naturally occurring nerve action potentials.

OFF Time: a period of time during a therapy algorithm where electrical blocking is stopped.

ON Time: a period of time during a therapy algorithm where an amplitude modulated electrical signal blocks the propagation of nerve action potentials.

ON/OFF cycle: the time period, in minutes, which encompasses one block-on time period and the one subsequent block-off time period.
**Daily treatment schedule**: the schedule during which the therapy algorithm is delivered within a 24-hour period as prescribed by the clinician (e.g., treatment begins at 7 am and continues until 11 pm).

**Ramp Up**: the time period, in seconds, required for the electrical output signal to reach the programmed amplitude when initiating an electrical blocking signal.

**Therapy**: the application of an electronic signal to a nerve in order to partially or completely block the propagation of naturally occurring nerve action potentials.

**Therapy algorithm**: the combination of specified parameters (amplitude, block on/block off cycle, frequency, and duration) used to define the electronic signal delivered to the vagal nerve trunks.

**Treatment compliance**: the percentage of time that the Maestro System delivers the daily treatment schedule as programmed by the clinician. Periods of non-compliance may be due to medical device malfunction, battery failure, or patient non-compliance with battery recharging.

### 10.2.3 Daily treatment schedule and therapy parameter selection

At implantation and initiation, the initial therapy settings will be standardized for all subjects. All subjects will have their devices initially set to an amplitude of 1 mA with a treatment schedule of 13 hours per day. The amplitude will be increased to 3 mA at the week 1 visit and will increase by 1 mA each following week reaching 6 mA at week 4. The programming sessions and the systematic amplitude increases will be performed for both treatment and control groups to maintain blinding. Subjects who cannot tolerate 3 mA at week 1 or 1 mA incremental increase will be increased at a slower rate and/or smaller increments. Therapy at 6 mA and 13 hour delivery schedule per day will be maintained for the remainder of the first 6 months.

Beyond the six month visit the therapy settings will be left unchanged if the subject is losing weight and is not experiencing unacceptable adverse events. On the other hand, if the subject is either not losing weight at an expected rate or is experiencing unacceptable adverse events, the therapy settings will be adjusted up or down as described below. The therapy settings for all subjects will be adjusted by a blinded coordinator.

#### 10.2.3.1 Therapy algorithm

The range of therapy parameters is provided in the table below.
Table 10.1. Therapy algorithm

<table>
<thead>
<tr>
<th>Fixed parameters</th>
<th>Parameter range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse width (µs)</td>
<td>90</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>5000</td>
</tr>
<tr>
<td>Ramp Down (secs)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjustable parameters</th>
<th>Parameter range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (mA)</td>
<td>1-8</td>
</tr>
<tr>
<td>Ramp Up (secs)</td>
<td>0-50</td>
</tr>
<tr>
<td>ON Time (mins)</td>
<td>2-5</td>
</tr>
<tr>
<td>OFF Time (mins)</td>
<td>5-10</td>
</tr>
<tr>
<td>Treatment schedule (hrs)</td>
<td>0 – 24</td>
</tr>
</tbody>
</table>

Note: when the therapy algorithm is set to 5 minutes ON, the system will deliver a 2 minute ON time followed by a 1 minute OFF period, followed by another 2 minute ON time. After this, the programmed OFF time will follow.

10.2.3.2. Impedance settings and adjustments

The Maestro RC2 System measures impedance prior to every programmed ON Time. This is a safety feature of the device and confirms operation of the system before delivering therapy. Some subjects have reported sensations when impedance is measured, while others have reported no sensations. These impedance measurements occur during acute patient acceptance testing and during programmed delivery of therapy. At the implantation and initiation visit the amplitude of the impedance measurement will be set to 1 mA. This parameter will be increased to 3 mA at the 1 week follow-up visit at the same time the therapy is increased to 3 mA. If the subjects report feelings of discomfort, the parameters for measuring impedance can be adjusted at therapy initiation or any time throughout the study. Table 10.2 below provides the parameters for impedance measurement.

Table 10.2. Impedance parameters

<table>
<thead>
<tr>
<th>Fixed parameters</th>
<th>Parameter range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse width (µs)</td>
<td>90</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>1000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjustable parameters</th>
<th>Parameter range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (mA)</td>
<td>1-3 (default is 3)</td>
</tr>
</tbody>
</table>

10.2.3.3. Therapy Initiation—acute patient acceptance testing therapy algorithm

All subjects will have their initial therapy set as described in Table 10.3 at implant.
### Table 10.3. Therapy Initiation-initial therapy algorithm

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (mA)</td>
<td>1</td>
</tr>
<tr>
<td>Ramp Up (secs)</td>
<td>20 (adjust as needed to facilitate subject acceptance)</td>
</tr>
<tr>
<td>ON Time (min)</td>
<td>5</td>
</tr>
<tr>
<td>OFF Time (min)</td>
<td>5</td>
</tr>
<tr>
<td>Impedance amplitude (mA)</td>
<td>1</td>
</tr>
<tr>
<td>Treatment schedule</td>
<td>13 hours per day, which results in approximately 12 hours therapy per day</td>
</tr>
<tr>
<td>Note: clinician sets the treatment schedule</td>
<td></td>
</tr>
</tbody>
</table>

Before the implant procedure, the site will review the subject’s normal waking hour schedule for each day of the week day and adjust the daily treatment schedule (recommended 13 hours per day) so therapy will be applied to cover these times (e.g., 8:00 am to 9:00 pm). The daily treatment schedule should be started and ended to maximize therapy during the subject’s waking hours for each day of the week and to provide therapy coverage for the subject’s major meals.

### 10.2.3.4. Post-Initiation therapy changes from Week 1 to Month 6

At the week 1 visit the amplitude will be adjusted. A five minute therapy algorithm test is performed and includes:

1. Adjusting the impedance measurement output parameter to 3 mA unless a subject has unacceptable discomfort during this measurement
2. Setting therapy amplitude parameter to 3 mA, or if not accepted by subject, lower to the highest level accepted by the subject without unacceptable discomfort

The subject will then have the therapy algorithm selected during the five-minute test applied for a minimum of 15 minutes. If this therapy algorithm is acceptable it can be used for the subject’s therapy algorithm.

At the week 2 through week 4 visits, amplitude for each subject will be adjusted up in 1 mA increments each week reaching 6 mA at week 4. In some cases it may be necessary to increase or decrease the Ramp Up setting in order to increase the amplitude. For those subjects who cannot tolerate the 1 mA increments, their amplitude will be increased more slowly. The algorithm for this process is illustrated in Figure 10.1.

Unless the subject reports unacceptable adverse events that are considered related to or possibly related to therapy settings, no other adjustments to therapy will be made during the first 6 months of treatment. If the subject reports unacceptable adverse events that are considered related to or possibly related to therapy, see section 10.2.3.6 for recommended actions.
During these visits the subject’s daily treatment schedule should be optimized to cover their normal waking hours. After reviewing the daily system use reports (from the Clinician Programmer) that detail subject compliance and system performance with subject, the daily treatment schedule can be refined to have therapy start and end at times during subject’s waking hours.

10.2.3.5. Therapy changes after month 6

First, optimize therapy

Before changing therapy it is important to establish and optimize subject compliance with recharging the system, to identify and resolve any system performance issues, and to find the highest accepted amplitude setting up to 6 mA. These factors can generally be established during the first four weeks after initiation. In some cases, it may take longer than 4 weeks to establish optimal subject compliance with recharging and system performance or these issues may develop later in the study.

In the first year, subjects who are losing weight at an expected minimum rate of 2.5 % EWL per month from their randomization visit as determined at prescribed visits should not have the therapy algorithm changed.

Changing the Therapy Algorithm

- Subjects who at any time in the trial are experiencing unacceptable adverse events considered related or possibly related to therapy can have their therapy algorithm adjusted as described in section 10.2.3.6 below.
- At the 6, 7, 8, 9, 10, and 11 month visits subjects will have their %EWL from implant compared with the expected rate of 2.5% EWL per month. This process is described in Figure 10.2.
  - If subjects do not meet the expected rate of loss, the subject’s therapy algorithm will be changed if the subject can tolerate the change and it is technically feasible. At month 6 this is set at 15% EWL. The month 7-11 target weights will be based on 2.5% EWL from the previous month’s weight.
  - If the subject loses at a rate greater than 2.5% EWL per month no change will be made.
  - Subjects who are at the monthly %EWL but gain weight from the previous month can have their therapy parameters adjusted.
- The primary therapy change will be to increase the output amplitude by 0.25 or 0.5 mA (recommend 0.5 mA) at each monthly visit where the expected rate of loss is not met until 8.0 mA or the highest tolerated output is reached.
- Once 8.0 mA or the highest tolerable output is reached the scheduled hours of therapy will be increased in 1 to 2 hour increments (2 hour recommended) until a maximum of 18 hours per day is reached.
- After the first year, the site personnel shall have discretion in looking at the past few months or only the last month when assessing therapy changes. The primary therapy change shall be to increase amplitude by 0.25 mA or 0.5 mA dependent on subject tolerability and technical feasibility of the system, with a maximum level of 8 mA. Changes in Ramp Up time can be made at the same time for subject acceptance of higher amplitudes. Hours of scheduled therapy can also be increased in 1 to 2 hour
increments not to exceed 18 hours of therapy per day. The process for this is outlined in Figure 10.3.
Figure 10.1. Algorithm for therapy change process during first 6 months

**Therapy Initiation at Implantation**
Set therapy output parameter and impedance output to 1.0 mA.
Keep all other parameters at default values.

**Therapy Adjustments**
Initially set amplitude to 3.0 mA and increase subject’s output current by 1 mA on a weekly basis until 6.0 mA or highest acceptable output is reached if less than 6.0 mA. Set impedance measurement amplitude to 3.0 mA if tolerated by the subject.

**Is therapy tolerated?**
- Yes
  - Therapy at 6 mA?
    - Yes
      - Maintain therapy at 6 mA and 13 hour delivery schedule per day for the remainder of the first 6 months.
    - No
      - Attempt to increase therapy output on a weekly basis at no more than 1.0 mA increase per week until the 6 mA level is reached. Use tolerability adjustments as needed.
  - No
    - Make Tolerability Adjustments (as needed)
      - Increase or Decrease Ramp Up time
      - Increase or Decrease output in smaller 0.5 mA steps
Figure 10.2. Algorithm for therapy change decision process during months 6 -11

Month 6, 7, 8, 9, 10, 11 Visit:
Determine subject’s %EWL from initiation.

Is %EWL at
15% at 6 mos
17.5% at 7 mos
20% at 8 mos
22.5% at 9 mos
25% at 10 mos
27.5% at 11 mos

Yes

Did subject have unacceptable weight gain from previous month?

No

Month 6:
Increase amplitude 0.25 or 0.5mA

Months: 7,8,9,10,11
Determine subject’s rate of %EWL from the previous month’s weight.

Is %EWL >2.5%

No

Change Therapy
Increase output by 0.25 mA or 0.5 mA to maximum of 8 mA. Or increase hours of use by 1 to 2 hours if an output limit has been reached. Use tolerability adjustments if needed.

Yes

Do not change parameters.
Maintain Therapy parameters

No
Figure 10.3. Algorithm for therapy change decision process after the first year

Follow-up Visits Month 12 and Beyond
Evaluate subject’s overall Excess Weight Loss and recent rate of %EWL over a one to two month period.

Is Overall %EWL acceptable?

No

At maximum allowed amplitude?

No

Increase Amplitude
Increase in 0.25 mA or 0.5 mA per month. Then monitor progress.

Yes

At maximum schedule of 18 hours per day?

Yes

Increase Therapy Schedule
Increase daily scheduled therapy by 1 or 2 hours with a maximum of 18 hours.

No

Maintain Therapy Settings
Continue to monitor and reevaluate progress at each scheduled visit.
10.2.3.6. **Therapy algorithm change for possible treatment-related adverse events**

If subjects are reporting unacceptable adverse events that are possibly related to therapy, the therapy algorithm can be changed at any time as described in the table below.

**Table 10.4, Therapy algorithm change for possible treatment-related events**

<table>
<thead>
<tr>
<th>Acceptable possible treatment-related events</th>
<th>Unacceptable possible treatment-related events</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continue with existing therapy settings</td>
<td>• Increase or decrease Amplitude</td>
</tr>
<tr>
<td></td>
<td>• Increase OFF Time</td>
</tr>
<tr>
<td></td>
<td>• Increase or decrease Ramp up</td>
</tr>
<tr>
<td></td>
<td>• Adjust daily treatment schedule</td>
</tr>
<tr>
<td></td>
<td>• Adjust impedance measurement</td>
</tr>
</tbody>
</table>

10.2.4 **Device interrogation and treatment compliance**

At all scheduled visits subsequent to initiation of treatment, as defined in Table 2.1 and Table 2.2, the Maestro RC2 System will be interrogated with the programmer. Doing this will upload all system performance, therapy delivery, and subject use data collected from the mobile charger to the programmer. Data from this interrogation will be used to assess system performance and subject compliance with recharging the system. Periods of non-compliance may be due to one or more of the following categories with the potential causes described:

- Lead impedance is out of range
- Low or no battery charge

After each visit with a programming change or device interrogation the Investigator will send the data to the Sponsor using the programmer’s automated data transfer feature (if possible) or by an alternate method.

10.2.4.1. **Short-term diagnostic assessment**

The Maestro RC2 System delivers the therapy wave form from the anterior lead tip electrode to the posterior lead tip electrode. Additionally, the system has been designed to have an option to deliver the therapy wave form from the ring electrode of each lead to the tip electrode of the same lead. The therapy wave form delivered into the vagal nerve trunks is identical in both of these configurations.

There may be specific situations when questions arise about system performance, lead integrity, high or low impedance, or subject discomfort with the use of the system which may limit their ability to accept desirable levels of current amplitude. In some of these
cases, it may be helpful to isolate the issue to one or both leads in order to guide the investigator to determine the best course of action to take, if any, to address the issue.

**Methods**
The diagnostic test described below is only to be performed as an acute test, under the supervision of the clinician and requires the presence of EnteroMedics personnel to enable the Clinician Programmer to apply this test. This test will only be done after all other diagnostic algorithms as detailed in the clinical investigational plan have been tried unsuccessfully. This test will be done only by unblinded study personnel.

**Diagnostic test**
This short-term diagnostic test utilizes the existing set of therapy parameters (included in Table 10.5 for reference).

<table>
<thead>
<tr>
<th>Table 10.54 Diagnostic parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed parameters</strong></td>
</tr>
<tr>
<td>Pulse width (µs)</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
</tr>
<tr>
<td>Ramp down (secs)</td>
</tr>
<tr>
<td><strong>Adjustable parameters</strong></td>
</tr>
<tr>
<td>Amplitude (mA)</td>
</tr>
<tr>
<td>Ramp up (secs)</td>
</tr>
<tr>
<td>ON Time (mins)</td>
</tr>
<tr>
<td>OFF Time (mins)</td>
</tr>
</tbody>
</table>

**Application of diagnostic test**
In order to maintain objective responses to the test conditions, the actual amplitude settings applied during diagnostic testing will not be communicated to the subject. The diagnostic testing will be performed with selected amplitudes consistent with the subject’s current amplitude setting. Testing may be done at higher amplitude settings, if needed, in the following sequence.
### Table 10.65 Diagnostic testing sequence

<table>
<thead>
<tr>
<th>Test number</th>
<th>Lead test configuration</th>
<th>Amplitude setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1 (baseline)</td>
<td>Anterior tip to posterior tip</td>
<td>Subject’s current setting</td>
</tr>
<tr>
<td>Test 2</td>
<td>Anterior tip to ring</td>
<td>0 mA&lt;br&gt;1&lt;sup&gt;st&lt;/sup&gt; desired mA&lt;br&gt;2&lt;sup&gt;nd&lt;/sup&gt; desired mA&lt;br&gt;3&lt;sup&gt;rd&lt;/sup&gt; desired mA</td>
</tr>
<tr>
<td>Test 3</td>
<td>Posterior tip to ring</td>
<td>0 mA&lt;br&gt;1&lt;sup&gt;st&lt;/sup&gt; desired mA&lt;br&gt;2&lt;sup&gt;nd&lt;/sup&gt; desired mA&lt;br&gt;3&lt;sup&gt;rd&lt;/sup&gt; desired mA</td>
</tr>
<tr>
<td>Test 4 (optional)</td>
<td>As determined by clinician and EnteroMedics personnel at time of testing&lt;br&gt;1&lt;sup&gt;st&lt;/sup&gt; desired mA&lt;br&gt;2&lt;sup&gt;nd&lt;/sup&gt; desired mA&lt;br&gt;3&lt;sup&gt;rd&lt;/sup&gt; desired mA&lt;br&gt;4&lt;sup&gt;th&lt;/sup&gt; desired mA</td>
<td></td>
</tr>
</tbody>
</table>
11.0 Schedule of trial events

Please refer to Table 2.1 for an overview of the schedule of trial events from Screen through 12 Months and Table 2.2 for an overview of the schedule of trial events from 12 months through 60 months follow-up.

11.1 Informed consent

The Investigator (or his/her designated assistant) will explain to each potential subject the nature of the trial, its purpose, procedures, expected duration, alternative options available and the benefits and risks involved in trial participation. Each subject will be given the opportunity to ask questions and will be informed of his/her right to withdraw from the trial at any time without prejudice. After this explanation and before entering the trial, the potential subject will voluntarily sign the informed consent statement approved by the Sponsor and IRB in the presence of a witness.

11.2 Screening period

Screen Period

After completing the informed consent process, all potential subjects will complete the following procedures during the screening period to determine eligibility for implant:

- Assess all inclusion and exclusion criteria
- Measure height (to determine BMI)
- Measure body weight
- Psychological assessment
- Complete medical history
- Complete physical examination
- Medication use assessment
- Measure waist and hip circumference
- Measure vital signs (blood pressures measured and recorded three times)
- Blood draw for clinical laboratory tests (fasted overnight)
- Urine pregnancy test (for women of child bearing potential)
- Subject questionnaires
- 7 day diet diary
- 12 lead ECG
- Device overview and training

Subjects who meet the initial requirements of the trial during Screening will be scheduled to have a barium swallow (upper GI x-ray) or upper endoscopy (esophagogastroduodenoscopy) per PI discretion.
11.3 Implant/Randomization/Initiation

11.3.1 Pre-operative preparation
Subjects are to report to the implant visit fasted overnight or follow the normal standard of care procedures. Each subject will complete the following procedures prior to surgery:

- Negative urine pregnancy test within 14 days of surgery (for women of child bearing potential)
  - Subjects with a positive urine pregnancy test will not be implanted with the Maestro System and will be exited from the trial
- Medication use assessment
- Adverse events assessment

Conduct the following procedures within 7 days prior to implant at the same visit:

- Measure body weight
- Measure vital signs

11.3.2 Surgical preparation
Subject will be prepped for surgery in accordance with local institution procedures.

Patient Infection Control recommendations
Follow standard of care procedures at institution

11.3.3 Maestro System implant/system testing/initiation
Prior to implant the randomization assignment will be selected.

The specific technique for surgical placement of the Maestro RC2 System, the sham surgical procedure and system testing is described in Maestro System Obesity Management System Implant Procedure Guide (provided separately).

RC2 System surgical procedure:

- Place leads using standard laparoscopic technique under anesthesia
- Place the neuroregulator in subcutaneous pocket located on the thoracic side wall
- Initiate therapy at 1 mA

Sham surgical procedure:

- Perform a sham surgical procedure that consists of the same number of incisions the investigator would use with general laparoscopic technique. For control patients, up to five incisions will be created, through the skin layer only, to simulate 5 mm trocar placement. These incisions may require wound care (e.g., bandages) and thus all subjects will have the same number of surgical incisions following surgery
- The control subjects will receive anesthesia similar to the treatment group
• The control subjects will be implanted with a non-functional neuroregulator which will be placed in a pocket in the same location as the functional neuroregulator. The sham neuroregulator will be designed using resistors that dissipate charge in a similar manner as the active neuroregulator. The battery in the sham device will deplete in the same fashion as the active device and will interact with the programmer in the same way as the active device.

• Initiate therapy at 1 mA

11.3.4 Immediate post-operative methods
Subjects will be carefully observed during the immediate postoperative period for bleeding and treated as needed.

As needed, pre-discharge device impedance check may be completed for some subjects at the request of the Sponsor or Investigator.

11.4 One week visit
Subjects will return to the investigator 7 ± 3 days after the device implant. At this visit the following procedures will be completed:

• Remove external sutures if appropriate
• Medication use assessment
• Adverse events assessment
• Measure body weight
• Measure vital signs
• Subject blinding assessment
• Weight management visit (first visit)
• 7 day diet and activity assessment
• Set Maestro System parameters as described in section 10.2.3.3
• Train subject on Maestro System use (see Maestro System Patient Instructions)
• Connect clinician programmer to internet/local area network and send data to EnteroMedics (if possible).

11.5 Treatment period follow-up visits

11.5.1 Follow-up visits
Subjects will return to the investigator at the weeks and visits noted in Table 2.1 and Table 2.2 to complete the following assessments:

Completed at all follow-up visits:

• Medication use assessment
• Adverse events assessment
• Measure body weight
• Measure vital signs (blood pressures measured and recorded three times at 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 month visits)
• Device interrogation
• Weight management (as described in section 10.1)
• 7 day diet and activity assessment
• Review system performance, and treatment programming adjustment, as needed (see section 10.2.3)
• Review subject compliance with recharging the system and retrain as needed (see section 10.2.3)
• Connect clinician programmer to internet/local area network and send data to EnteroMedics (if possible).
• Subject blinding assessment (months 6, and 12)
• 12 lead ECG (months 4, 8, and 12)
• Subject Questionnaires (months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60)
• Measure waist and hip circumference (months 6, 12, 24, 36, 48, and 60)
• Fasting blood draw for clinical laboratory tests (months 6, 12, 24, 36, 48, and 60)
• Blinding status (week 1, 6 and 12 months)
• Subject self assessment,
  o food choices/calorie goal
  o weight status
  o enthusiasm of participation in study

**Completed only at 12 month follow-up visit:**

- Each subject will be asked which treatment group he/she believes they were assigned, or if they “don’t know”. If a subject terminates the trial prior to the 12 month follow-up visit the subject will be asked to which group they believed they were assigned or if they “don’t know”.
- After the required evaluation procedures are completed at the 12-month visit, all subjects who continue in the trial will have the opportunity to receive therapy after they are unblinded to their treatment assignment. The control subjects will require a second surgery to have an operational device implanted. Every effort will be made to use the same incision sites created to implant the RC2 system. Therapy initiation for these subjects will be performed as described in section 10.2.3.3 and subjects will follow the same visit schedule as year one. If the control subject decides not to have therapy and withdraw from the study a second operation will be required to remove the sham neuroregulator.

**11.5.2 Follow-up visits for sham surgical group after 12 months**

Prior to the implantation of the active RC2 system subjects will continue to follow year two regular scheduled visits. Once the active RC2 System has successfully been implanted, subjects will follow the same visit schedule as year one:

- Weekly visits for the first 4 weeks
- Every two weeks from 4 weeks to 12 weeks
- Monthly visits for an additional 8 months
- Telephone contact through six months
Subjects who were randomized to the control group will be followed for a total of 5 years.

11.5.3 Telephone contact

After the Week 12 visit and once between every scheduled trial visit through six months the Investigator or designee will attempt to contact subjects by telephone to review questions and identify and resolve any issues subjects may have with using the Maestro System. The outcome of the telephone contact will be documented on the appropriate case report form.

11.5.4 Unscheduled visits

Subjects may return to the Investigator at any time for assessing a medical concern or adverse event or for the purpose of assessing therapy changes as described in section 10.2.3.5. If a subject returns for an unscheduled visit, this visit should be documented, along with applicable procedures as determined by the investigator.

11.6 Trial exit visit

All subjects who completed the implant procedure and who will exit the trial prior to completing all scheduled visits will have a final assessment of the following items:

- Medication use assessment
- Adverse events assessment
- Measure body weight
- Measure vital signs
- Measure waist and hip circumference
- Blood draw for clinical laboratory tests (fasted overnight)
- Physical examination
- 12 lead ECG (if exit prior to 12 months)
- Subject’s assessment of treatment group assignment or if they “don’t know” (if exit is prior to 12 months)
- Subject questionnaires (if not completed within the last month)
- System removal/deactivation (neuroregulator, cap lead or explant as medically indicated, see section 11.6.1 if applicable)
  
  Note: any adverse events occurring at the time of system removal will be collected and recorded on the appropriate case report form.

The trial exit visit and procedures should occur after device removal is completed. In cases where a subject has decided to leave the trial but does not want to have the device removed, the trial exit procedure should be completed (or scheduled) at the time the decision to exit has been made. If there is an SAE that is ongoing after device removal, the trial exit visit should be completed after the SAE is resolved or the investigator has determined follow-up is no longer required.

If a subject assigned to the control group wishes to exit the trial and does not wish to receive active treatment, the sham device will be removed by the unblinded implanting surgical team.
If a subject has expressed a desire to exit the trial or has planned to exit the trial, the subject should be encouraged to continue regularly scheduled follow-up visits, completing as many of the protocol-required procedures as possible, until the device is removed and the trial exit visit has been completed.

11.6.1 System Removal

The Maestro System implantable components (Model 2002 Neuroregulator and Model 2200 Lead series) are biocompatible and intended for long-term implant. EnteroMedics intends to follow subjects for up to 5 years of follow-up as part of the clinical study. EnteroMedics intends to support the Maestro System for that period of time.

If a subject is losing weight and wishes to interrupt therapy during the trial and continue therapy at a later date, the neuroregulator and leads can and should remain implanted. The device should be programmed to stand-by mode. The subject would be asked to return the mobile charger and transmit coil so that the implanted system would remain inactive. Therapy could be re-initiated when desired using the existing leads and neuroregulator by visiting the clinician to have the device re-initiated to provide therapy and provide the subject with the mobile charger and transmit coil.

At the conclusion of the trial or for any medical reason in which system explantation is required, the neuroregulator can be removed under anesthesia. The implanted leads should also be removed if possible or the lead length shortened.
12.0 Data Safety Monitoring Board (DSMB) and Clinical Events Committee (CEC)

An independent Data Safety Monitoring Board (DSMB) will be established prior to the initiation of the trial. Members will represent internal medicine, bariatric surgery, and gastroenterology. The DSMB will meet regularly to assess the ongoing safety information collected during the trial. The DSMB will have access to the blinding schedule as needed for evaluation of adverse events. The functions of the DSMB are as follows:

- Develop a charter
- Conduct regular teleconferences to make assessments (e.g. futility) and recommendations
- Benchmark against adverse event profiles from other relevant device development programs (e.g., LAP-Band®, REALIZE and Cyberonics registration trials)

Members of the DSMB will also function as the Clinical Events Committee (CEC). The CEC will be responsible for adjudicating all serious adverse events. The CEC will determine whether the event is a Serious Adverse Event (SAE) and if it is a SAE whether the event is an Unanticipated Adverse Device Effect (UADE) and whether the origin of the SAE is from a pre-existing condition, general surgical procedure (e.g. anesthesia administration and not the implant procedure), implant/revision procedure, device, therapy or other/not related.
13.0 Data and quality management

13.1 Case report forms
Standardization of data collection and audit trail will be achieved through the use of an electronic data capture system using electronic case report forms (eCRFs), which will be completed for each patient. All information recorded on the forms must be supported by documentation in the subject’s file (clinic or hospital records). The subject file should include (but is not limited to) the following:

- an entry stating that the subject signed an informed consent form prior to entry into the trial and is participating in the trial
- subject ID
- diagnosis
- entries for all therapy/medications
- entries summarizing all clinic visits, including those for trial purposes
- entries for all adverse events

The monitor will verify eCRF entries against subject records. eCRFs and all supporting information should be readily available for review during scheduled monitoring visits.

A final copy of the eCRF will be provided to the investigator for retention at the investigator’s site.

13.2 Monitoring
The clinical monitor is appointed by the Sponsor and is responsible for assessing the Investigator’s compliance with the clinical investigational plan and for performing source-data verification.

The clinical monitor will also visit each investigative site at routine intervals throughout the trial. During these visits the clinical monitor will complete some or all of the following activities:

- review the clinical investigational plan
- conduct any necessary training
- assist with technical issues and/or questions about the Maestro System
- review the progress of the trial
- assess whether the trial records are complete
- assess compliance with the clinical investigational plan
- verify the data entered on the eCRFs against the source records

A close-out visit will be scheduled after the last subject at a particular site has completed participation in the trial and all data have been recorded on the eCRFs. During the close-out visit the clinical monitor will complete the following activities:
• Source verify all remaining eCRFs
• conduct a final inventory of Maestro System components
• return any unused Maestro System components
• review the trial record for completeness
• explain the record retention policy

After the close-out visit, the Sponsor may request additional information to support the clarification and/or correction of clinical data entries.

13.3 Device accountability
The Investigator shall maintain a log of all investigational devices received, used, and returned to the Sponsor. All investigational devices will be stored in a secure cabinet or room until it is used in the clinical trial. At the end of the trial all investigational devices will be returned to the Sponsor. Any explanted device or device opened but not used shall be returned to the Sponsor promptly.

13.4 Central clinical laboratories
An accredited, central clinical laboratory approved by the Sponsor, will perform all laboratory assays. Manuals detailing collection methodology sample handling and current laboratory certifications and normal reference ranges will be provided to each site.

13.5 Training
All Investigators and co-investigators will be trained on this investigational plan prior to their involvement in this trial. Training will be documented on the appropriate training log.

13.6 Subject identification
An electronic log will be maintained by the Investigator via the eCRFs. The following information will be recorded for all subjects who are enrolled:

• subject ID
• date subject signed the informed consent form
• date of screening visit

For subjects not enrolled the following information will be recorded in a screening log:

• screening number
• reason for exclusion

13.7 Amendments to the clinical investigational plan
The study Sponsor may request that the Investigator submit a supplemental protocol for institutional review board consideration if Sponsor or an Investigator proposes a change in the protocol that may affect its scientific soundness or the rights, safety, or welfare of subjects. These amendments should be signed by the Investigator and Sponsor and approved by the Ethics Committee before implementation and no protocol changes will
be implemented without, at a minimum, a 5-day notice being submitted to FDA, or if the change in the protocol may affect its scientific soundness or the rights, safety, or welfare of subjects, prior submission to and approval of the changes by FDA. These requirements do not apply in the case of a deviation from the protocol to protect the life or physical well being of a subject in an emergency; the deviation shall be reported to Sponsor within 5 days.

13.8 Early termination or suspension of the investigation

The entire trial or any trial site may be terminated if deemed necessary by the Sponsor. If the trial is terminated, those subjects who received treatment will be followed as though no termination had occurred.

The Investigator will complete and report the trial in satisfactory compliance with the clinical investigational plan. It is agreed that, for reasonable cause, either the Investigator or the Sponsor may terminate participation in the trial by providing written notice of termination submitted a reasonable time in advance of intended termination. If the trial is terminated for safety reasons, the Investigator will be notified immediately by telephone, followed by written instructions for trial termination.

13.9 Study report

Case report forms and additional subject/study data will be maintained and analyzed in a study database. A report will be written by the Sponsor regarding the outcome of the study and will be provided to the Investigators.
14.0 Responsibilities of the investigator

14.1 Introduction
This trial is subject to Good Clinical Practice (GCP) regulations and guidance issued by the Food and Drug Administration (FDA) and the International Organization for Standards (ISO) which are included in the following parts of the FDA Code of Federal Regulations (CFR) and ISO documents:

United States sites will follow:

- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 56: Institutional review boards
- 21 CFR Part 812: Investigational Device Exemptions
- 21 CFR Part 11: Electronic Records; Electronic Signatures
- 21 CFR Part 54: Financial Disclosure by Clinical Investigators

All Sites will follow:

- ISO 14155-1: Clinical Investigation of Medical Devices for Human Subjects – Part 1: General Requirements

Outside the United States sites will follow:

- Local laws

The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical studies that have been developed by the medical, scientific and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not
- the study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings
- the potential benefits of the research justify the risks

EnteroMedics is the trial Sponsor and is responsible for the following:

- selecting qualified Investigators
• providing Investigators with the information they need to properly conduct an investigation
• ensuring proper monitoring of the investigation
• ensuring that the study is conducted according to the clinical investigational plan,
• ensuring that regulatory agencies and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the device being studied

As an Investigator, you are responsible for ensuring that the trial is conducted according to the signed Investigator Agreement, the clinical investigational plan, and all applicable regulations. You are responsible for protecting the rights, safety and welfare of subjects under your care and for the control of the devices under investigation.

The rest of this section of the clinical investigational plan describes in more detail the specific GCP-defined responsibilities you assume by agreeing to participate in this study.

14.2 Protection of human subjects

14.2.1 Institutional review board approval
The Investigator must submit the clinical investigational plan and patient informed consent form to the institutional review board and obtain written approval from any applicable regulatory agencies before participating in the trial. The Investigator is also responsible for fulfilling any conditions of approval imposed by the institutional review board and/or other applicable regulatory agencies, such as reporting of serious adverse events, progress reports, etc.

14.2.2 Informed Consent
The Investigator (or designee) will explain to each potential subject the nature of the trial, its purpose, procedures, expected duration, alternative options available and the benefits and risks involved in trial participation. Each potential subject will be given the opportunity to ask questions and will be informed of his/her right to withdraw from the trial at any time without prejudice. After this explanation and before entering the trial, the potential subject will voluntarily sign an informed consent statement in the presence of a witness if he/she agrees to participate.

14.2.3 Protection of subject data
The Investigator (or his/her designee) is responsible for keeping a record of all enrolled subjects including full names and last known addresses. All subjects will be identified in the case report forms (CRFs) by their subject ID number and, unless local law prohibits, their initials. Additionally the Clinician Programmer will identify subject by their subject ID number.

14.2.4 Health Insurance Portability and Accountability Act (HIPAA)
HIPAA requires using and providing patient confidentiality and privacy practices. HIPAA provides standards for security of health information. The Investigator will acquire, either separately or within the Informed Consent document, the appropriate
authorization to use and disclose health information from each subject in accordance with HIPAA. See information for an example authorization statement.

HIPAA gives patients specific rights:

- Patients have the right to adequate notice of privacy practices
- Patients have the right to ask for privacy protection for protected health information (PHI)
- Patients have the right to inspect and have copies made of health care information, including medical records and billing information
- Patients also have the right to request an amendment of Protected Health Information
- Patients have a right to an Accounting of Disclosures
- Patients have a right to rescind their authorization

14.3 Reports

The Investigator is responsible for the following reports:

- Serious adverse events and potential unanticipated adverse device effects. Which must be reported to the sponsor within 72 hours of learning of the event. Additionally, notification to the institutional review board of any UADEs should be done as soon as possible, but no later than ten working days, after learning of the event. Reporting SAEs to the institutional review board is not required by FDA regulations, but it may be required as determined by each institutional review board
- Withdrawal of institutional review board approval (to be reported to the Sponsor within five working days)
- Progress reports (provided to the sponsor and institutional review board at regular intervals but no less than yearly)
- Deviations from the protocol to protect the life or physical well-being of a subject in an emergency need to be reported to the sponsor and institutional review board as soon as possible but no later than five working days. Except in an emergency, prior approval from the sponsor is required for changes in or deviations from the clinical investigational plan, if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects
- Use of the investigational device without informed consent (to be reported to the sponsor and the institutional review board within five working days after the use occurs)
- A final report (to be provided to the sponsor and institutional review board within 30 days after termination or completion of the investigation)
- Other trial-related reports (upon request by a reviewing institutional review board and/or regulatory agency)
14.4 Trial records and archives

Trial records will be maintained at the trial center and with the Sponsor (or their designee). Access to files, removing files, and photocopying files is restricted to the Sponsor (or designee), regulatory agencies, the Investigator (or designee), and the clinical monitors. The records will be kept in a manner to assure security against loss. All records pertaining to the trial will be archived two years after the conclusion of the trial unless notified by the Sponsor that they should be maintained longer.

The Investigator is responsible for maintaining the following records for a period of two years following the termination or completion of the trial or longer if notified by the Sponsor to do so:

- All trial-related correspondence with a institutional review board, another investigator, Sponsor, Monitor, and regulatory agencies, including required reports
- Records of receipt, use, and disposition of the test device system, including receipt dates, lot numbers, who used and received the device, and why and how many of the devices were returned to the Sponsor or otherwise disposed of
- Records of each subject’s case history, including all trial-required eCRFs, evidence of informed consent, all relevant observations of adverse events, the results of diagnostic testing, and the date of each study treatment
- Clinical investigational plan including documented dates and reasons for each deviation from the clinical investigational plan

14.5 Inspections

It may be necessary for the sponsor and/or a regulatory agency to audit the investigational site. The purpose of an audit is to assess the accuracy, adequacy and consistency of the study records and subject data and to assess adherence to the procedures described in this clinical investigational plan. Audits usually take approximately two days. A typical audit visit will include the following:

- upon arrival, an interview with the investigator and study personnel
- a tour of the facility
- a review of the trial records
- a review of the case report forms and source documents
- at the conclusion of the audit, a discussion of any key audit observations

If the sponsor selects an investigational site for an audit, the clinical monitor will schedule the visit and assist the investigator in preparing for the audit.

If a regulatory agency selects an investigational site for an audit, the investigators will immediately notify the clinical monitor. The clinical monitor will assist the investigator to prepare for the audit.
15.0 Publication policy

The Investigator reserves the right to publish and/or present the results of the clinical trial and related information. However, before publishing or presenting data, the principal investigator agrees to submit copies of any and all proposed manuscripts to Sponsor at least 30 days in advance of submitting such proposed manuscripts to a publisher or other third party to evaluate the proposed manuscript:

- for accuracy and consonance with the Sponsor’s database
- to ascertain whether confidential information or other proprietary information of Sponsor (including trade secrets and patent protected materials) is being inappropriately utilized and/or released
- to provide the Investigator with information which may not yet be available to them and
- to provide input from other investigators and co-investigators in the trial, if any, regarding the content and conclusions of the proposed manuscripts

If the Sponsor makes a good faith determination, within such 30-day period, that the publication or presentation would be detrimental to its intellectual property interests, Investigator shall refrain from submitting such proposed manuscript to a publisher or other third party for another 90 days to allow the Sponsor to file patent applications or take other steps to protect its intellectual property interests or, in the alternative at the Sponsor’s election, shall redact or otherwise modify the proposed manuscript to remove any language that the Sponsor believes in good faith to be detrimental to Sponsor’s or its affiliated entities’ intellectual property interests. The Investigator further agrees to redact or modify those sections of the proposed manuscript which the Sponsor reasonably and in good faith determines inaccurately reflect the results of the trial.

The foregoing notwithstanding, the Investigator acknowledges that this is a multi-center Trial and that the Sponsor has an interest in ensuring that a multi-center publication is the first publication to be released or presented regarding the completed trial. The Investigator agrees that they shall not independently publish or present any materials regarding the completed Trial until such a multi-center publication is released. The multi-center publication for the Trial shall be coordinated by the Sponsor.
16.0 Appendix A: Metropolitan height and weight tables for men and women on metric basis according to body frame size, ages 25-59 in indoor clothing

<table>
<thead>
<tr>
<th>Women (medium frame)</th>
<th>MEN (medium frame)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEIGHT (In Shoes)+</td>
<td>WEIGHT</td>
</tr>
<tr>
<td>Centimeters</td>
<td>Kilograms</td>
</tr>
<tr>
<td>148</td>
<td>49.6 - 55.1</td>
</tr>
<tr>
<td>149</td>
<td>50.0 - 55.5</td>
</tr>
<tr>
<td>150</td>
<td>50.3 - 55.9</td>
</tr>
<tr>
<td>151</td>
<td>50.7 - 56.4</td>
</tr>
<tr>
<td>152</td>
<td>51.1 - 57.0</td>
</tr>
<tr>
<td>153</td>
<td>51.5 - 57.5</td>
</tr>
<tr>
<td>154</td>
<td>51.9 - 58.0</td>
</tr>
<tr>
<td>155</td>
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<td>57.5 - 63.9</td>
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<td>58.1 - 64.5</td>
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<td>167</td>
<td>58.7 - 65.0</td>
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<tr>
<td>168</td>
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<td>169</td>
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<td>60.2 - 66.6</td>
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<tr>
<td>171</td>
<td>60.7 - 67.1</td>
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<td>61.8 - 68.2</td>
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<td>181</td>
<td>66.1 - 72.5</td>
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<td>182</td>
<td>66.6 - 73.0</td>
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<td>183</td>
<td>67.1 - 73.5</td>
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* Indoor clothing weighing 2.3 kilograms for men and 1.4 kilograms for women.
+ Shoes with 2.5 cm heels
17.0  **Appendix B: Weight management – Year One outline and Year Two outline**

<table>
<thead>
<tr>
<th>ReCharge Study Weight Management Individual Sessions</th>
<th>17 sessions total over 1 year</th>
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<tbody>
<tr>
<td><strong>Session #</strong></td>
<td><strong>Session Title &amp; Topics</strong></td>
</tr>
<tr>
<td><strong>First Four Weeks – Weekly Meetings (4 sessions)</strong></td>
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</tr>
<tr>
<td>1</td>
<td>Introduction</td>
</tr>
<tr>
<td>2</td>
<td>Healthy food choices</td>
</tr>
<tr>
<td>3</td>
<td>Take charge of what's around you</td>
</tr>
<tr>
<td>4</td>
<td>Physical activity - barriers to exercise</td>
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<tr>
<td><strong>Next 11 months (Subject to complete sessions in order)</strong></td>
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</tr>
<tr>
<td>5</td>
<td>Stress and weight loss</td>
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<tr>
<td>6</td>
<td>Mindful eating</td>
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<td>7</td>
<td>Physical fitness</td>
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<tr>
<td>8</td>
<td>Eating patterns</td>
</tr>
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<td>9</td>
<td>Keys to healthy eating in restaurants</td>
</tr>
<tr>
<td>10</td>
<td>Managing slips and lapses</td>
</tr>
<tr>
<td>11</td>
<td>Eating in social situations/holidays</td>
</tr>
<tr>
<td>12</td>
<td>Assertiveness &amp; social support</td>
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<tr>
<td>13</td>
<td>Strength training</td>
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<td>14</td>
<td>Healthy cooking</td>
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<tr>
<td>15</td>
<td>Reaching a plateau</td>
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<tr>
<td>16</td>
<td>Fiber</td>
</tr>
<tr>
<td>17</td>
<td>Motivation over the long term</td>
</tr>
<tr>
<td>Session #</td>
<td>Session Title &amp; Topics</td>
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<tr>
<td>----------</td>
<td>----------------------------------------------------</td>
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<td>18</td>
<td>Portion distortion</td>
</tr>
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<td>19</td>
<td>Finding time to be active</td>
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<tr>
<td>20</td>
<td>Thoughts and weight control</td>
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<td>21</td>
<td>Eating fewer calories without getting hungry</td>
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<td>22</td>
<td>Fad diets</td>
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<td>23</td>
<td>Problem solving</td>
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<td>Meal planning</td>
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<td>25</td>
<td>Staying motivated to keep exercising</td>
</tr>
<tr>
<td>26</td>
<td>Fast food/Eating out</td>
</tr>
<tr>
<td>27</td>
<td>Vitamins and minerals</td>
</tr>
<tr>
<td>28</td>
<td>Staying active on holidays and vacations</td>
</tr>
</tbody>
</table>
18.0 References

41 Bray et al. Is it time to change the way that we report and discuss weight loss? Obesity 2009; Apr17(4):619-621.