

## Original Investigation

# Effect of Reversible Intermittent Intra-abdominal Vagal Nerve Blockade on Morbid Obesity

## The ReCharge Randomized Clinical Trial

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**IMPORTANCE** Although conventional bariatric surgery results in weight loss, it does so with potential short-term and long-term morbidity.

**OBJECTIVE** To evaluate the effectiveness and safety of intermittent, reversible vagal nerve blockade therapy for obesity treatment.

**DESIGN, SETTING, AND PARTICIPANTS** A randomized, double-blind, sham-controlled clinical trial involving 239 participants who had a body mass index of 40 to 45 or 35 to 40 and 1 or more obesity-related condition was conducted at 10 sites in the United States and Australia between May and December 2011. The 12-month blinded portion of the 5-year study was completed in January 2013.

**INTERVENTIONS** One hundred sixty-two patients received an active vagal nerve block device and 77 received a sham device. All participants received weight management education.

**MAIN OUTCOMES AND MEASURES** The coprimarily efficacy objectives were to determine whether the vagal nerve block was superior in mean percentage excess weight loss to sham by a 10-point margin with at least 55% of patients in the vagal block group achieving a 20% loss and 45% achieving a 25% loss. The primary safety objective was to determine whether the rate of serious adverse events related to device, procedure, or therapy in the vagal block group was less than 15%.

**RESULTS** In the intent-to-treat analysis, the vagal nerve block group had a mean 24.4% excess weight loss (9.2% of their initial body weight loss) vs 15.9% excess weight loss (6.0% initial body weight loss) in the sham group. The mean difference in the percentage of the excess weight loss between groups was 8.5 percentage points (95% CI, 3.1-13.9), which did not meet the 10-point target ( $P = .71$ ), although weight loss was statistically greater in the vagal nerve block group ( $P = .002$  for treatment difference in a post hoc analysis). At 12 months, 52% of patients in the vagal nerve block group achieved 20% or more excess weight loss and 38% achieved 25% or more excess weight loss vs 32% in the sham group who achieved 20% or more loss and 23% who achieved 25% or more loss. The device, procedure, or therapy-related serious adverse event rate in the vagal nerve block group was 3.7% (95% CI, 1.4%-7.9%), significantly lower than the 15% goal. The adverse events more frequent in the vagal nerve block group were heartburn or dyspepsia and abdominal pain attributed to therapy; all were reported as mild or moderate in severity.

**CONCLUSION AND RELEVANCE** Among patients with morbid obesity, the use of vagal nerve block therapy compared with a sham control device did not meet either of the prespecified coprimarily efficacy objectives, although weight loss in the vagal block group was statistically greater than in the sham device group. The treatment was well tolerated, having met the primary safety objective.

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Illness imposed by obesity, especially by morbid obesity, has inspired an array of treatment options, typically applied in stepwise fashion. Although changes in food intake and activity levels can be effective for some, the mean effect is modest.<sup>1</sup> The most effective treatment, bariatric surgery, can produce significant weight loss and improvement in health but is associated with risks of morbidity and distortion of anatomy that are unacceptable to some.<sup>2</sup> Medications can be helpful, but their application is limited by adverse effects and reluctance of insurance companies to cover them.<sup>3</sup> There is great interest in the development of a device that could be as effective or nearly as effective as bariatric surgery but that has fewer risks and that is less invasive. One such possibility is vagal blockade using electrodes implanted through minimally invasive laparoscopic surgery.<sup>4</sup>

The vagus nerve is known to play a key role in satiety, metabolism, and autonomic control in upper gastrointestinal track function.<sup>5</sup> The EMPOWER<sup>6</sup> study, a recent randomized trial testing vagal blockade, found substantial weight loss, but the difference in weight loss between treatment and control groups was not significant. However, treatment group participants who received at least 12 hours of vagal block therapy a day achieved the level of weight loss anticipated in the design. Furthermore, a significant dose response of weight loss in relation to hours of device use for both groups coupled with the possibility that control patients may have received partial vagal blockade through low-energy safety or device checks confounded the interpretation of the trial's results.<sup>6</sup> These findings required a new study to determine the efficacy of vagal nerve block therapy with a treatment device that consistently delivered at least 12 hours of therapy a day and a sham control device that had no possibility of delivering therapy. The ReCharge Study, a multicenter, randomized, double-blind trial that addressed these design limitations, is the focus of this article.

## Methods

### Participants

Participants at 2 sites in Australia and 8 sites in the United States were eligible for inclusion in the study if their body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) was 40 to 45 (class III obesity) or 35 to 40 (class II obesity) and had 1 or more obesity-related comorbid conditions, including type 2 diabetes, hypertension (systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg), dyslipidemia (total cholesterol  $\geq 200$  mg/dL or low-density lipoprotein [LDL]  $\geq 130$  mg/dL), sleep apnea syndrome, or obesity-related cardiomyopathy. The participation of those with type 2 diabetes was limited so that potential weight loss limiting effects of diabetes and its treatment did not affect the study outcomes. A detailed description of inclusion and exclusion criteria can be found in Supplement 1. All participants provided written informed consent, and the institutional review boards at each study site approved all study protocols. (To convert LDL from mg/dL to mmol/L, multiply by 0.0259.)

### Study Design

This multicenter, randomized, double-blind trial compared active vagal nerve blocking with an implanted sham device. The randomization allocation was 2:1 for active vagal nerve block to sham devices in permuted block sizes of 3 or 6, stratified by study site and type 2 diabetes status (Figure 1). To ensure comparability between groups with respect to potential weight loss, participants with type 2 diabetes were limited to 10% of enrollment at each site; their randomization was not stratified by site. Randomization to active or sham group occurred once patients were admitted to the hospital. The participant, sponsor, and follow-up staff at the clinical site were blinded to treatment assignment. The surgeons and surgery support staff could not be blinded, so their interaction with participants after placing the device was limited.

Implanting vagal nerve block therapy electrodes requires standard laparoscopic techniques and general anesthesia.<sup>4</sup> The anterior and posterior vagus nerves were identified and dissected free at the gastroesophageal junction. Customized electrodes were placed around the nerves and then secured with sutures.<sup>4</sup> These electrodes were connected to a transcutaneously rechargeable neuroregulator placed in a subcutaneous pocket on the thoracic side wall. Both treatment and control devices were 8.6 cm in diameter, 7.1 cm in width, and 1.6 cm thick.

Participants in the sham group were implanted similarly but with a neuroregulator that dissipated charges into an electronic circuit within the device without leads. Their procedure consisted of the same number of skin incisions as vagal nerve block participants without peritoneal penetration.

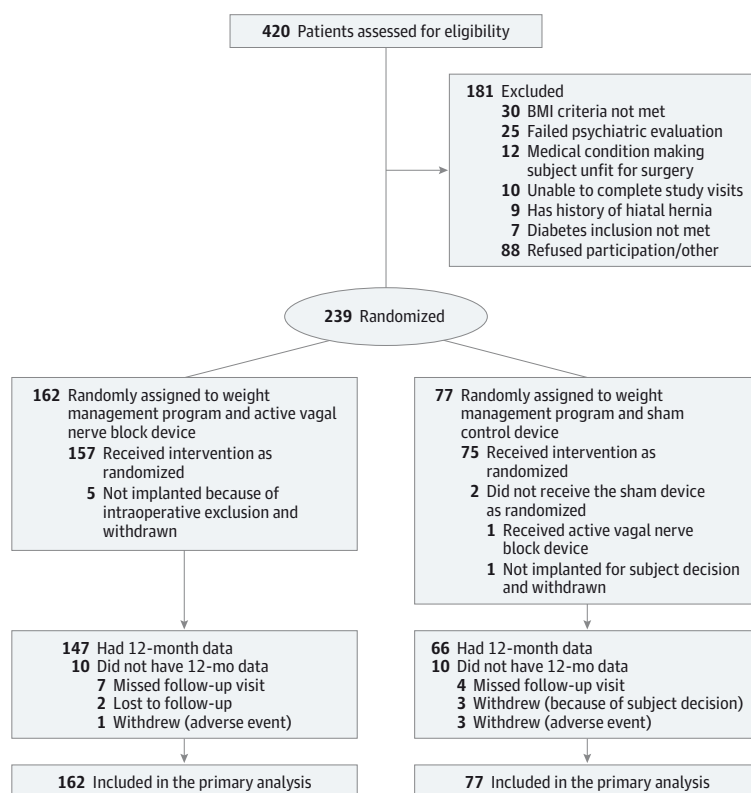
Neuroregulators were programmed to deliver a charge for at least 12 hours daily. An external programming device allowed the investigator to increase the amplitude in both active and sham devices at scheduled intervals during follow-up visits in accordance with the protocol to the desired amplitude of 6 to 8 mA, depending on patient tolerance. The active or sham neuroregulator battery required recharging at least twice a week for approximately 30 minutes to 90 minutes using an external charging device. Each charging session was recorded by the device and data were monitored by the clinic staff for safety and recharging adherence.

### Data Collection and Study Conduct

Data collected prior to randomization included height, weight, medical histories, and medication usage. Follow-up visits following randomization were weekly for the first month, then every 2 weeks between weeks 4 and 12, and monthly thereafter from 3 to 12 months to collect primary and secondary measures including weight and adverse events. All participants attended a weight management program, consisting of 17 face-to-face educational counseling sessions that ranged from 15 minutes to 45 minutes and discussed such topics as healthful food choices, physical fitness, and social support. No diet or exercise regimen was prescribed.

Coprimary efficacy objectives for the study were based on the percentage excess weight loss, which is calculated using

Figure 1. CONSORT Diagram of Participants in the ReCharge Study



BMI indicates body mass index.

the formula: percent of excess weight loss =  $100\% \times [\text{weight loss/excess body weight at implant placement}]$ . Excess body weight was defined as the difference between weight at implantation and the ideal body weight to achieve a BMI of 25. The first efficacy objective was based on a mean percent excess weight loss comparison between groups at a superiority margin of 10% (super-superiority). The second efficacy objective was to demonstrate that 55% of patients in the vagal nerve block group would achieve 20% excess weight loss and that 45% would achieve 25% excess weight loss.

Safety data were monitored by an independent data and safety monitoring board that was chartered to meet at least annually and adjudicated all serious adverse events. No interim analyses or early stopping boundaries were used during this study. Serious adverse events were defined as any untoward event that led to death or serious deterioration in the health of the participant, including prolonged hospitalization. The primary safety objective was to demonstrate that the serious adverse event rate related to the device, the implant or revision, or the therapy was less than 15% in the vagal nerve block group. This single-group comparison with a performance criterion was chosen in consultation with the US Food and Drug Administration (FDA) to demonstrate a lower serious adverse event rate than studies used to support FDA approval for the laparoscopic adjustable gastric band. The site investigator determined the severity and attribution of adverse events that were not serious.

### Statistical Analysis

The assumptions of the trial were that, on average, patients in the vagal nerve block group would achieve 25% excess weight loss and the sham group would achieve 5% excess weight loss at 12 months. These estimates were based on experience with the dose-response effect observed in the EMPOWER trial and the 12-month weight loss observed in the VBLOC DM2 study among participants with type 2 diabetes.<sup>6,7</sup> In EMPOWER, participants with fewer than 6 hours of device use per day in the first 12 months achieved a mean 5% excess weight loss, and those who received at least 12 hours of therapy per day achieved a mean 29% of excess weight loss.<sup>6</sup> In the observational VBLOC DM2 study, participants achieved an average of 25% of excess weight loss.<sup>7</sup> Therefore, it was determined that a minimum of 233 participants (allocated 2:1) would be required to achieve 85% statistical power to detect a 20-point mean difference between groups with a superiority margin of 10 points at 12 months, accounting for up to 15% attrition.

Data were analyzed according to the intention-to-treat (ITT) principle, in which all participants were analyzed as randomized. Per protocol, missing 12-month values for the percentage of excess weight lost were imputed using the last-observation-carried-forward method. We also conducted a post hoc multiple imputation analysis with 50 imputation data sets using multivariate normal regression for 26 missing 12-month values for the percentage of excess weight loss using

Table 1. Baseline Characteristics by Treatment Group

	Vagal Nerve Block (n=162)	Sham (n=77)
Demographics		
Women, No. (%)	141 (87)	62 (81)
Age, mean (SD), y	47 (10)	47 (9)
Race, No. (%)		
White	149 (92)	73 (95)
Black	8 (5)	3 (4)
American Indian	2 (1)	1 (1)
Asian	1 (1)	1 (1)
Hawaiian/Pacific Islander	1 (1)	0
Body size measures when device placed, mean (SD)		
Height, cm	166 (8)	168 (9)
Weight, kg	113 (13)	116 (14)
Body mass index	41 (3)	41 (3)
Excess weight, kg <sup>a</sup>	44 (9)	45 (10)
Waist circumference, cm	121 (12)	123 (11)
Type 2 diabetes mellitus, No. (%)	9 (6)	6 (8)
Hypertension, No. (%)	63 (39)	32 (42)
Dyslipidemia, No. (%)	91 (56)	46 (60)
Obstructive sleep apnea, No. (%)	33 (20)	23 (30)

<sup>a</sup> Excess weight was calculated as the difference between the weight at the time of implantation and the ideal body weight corresponding to a body mass index of 25, which is calculated as weight in kilograms divided by height in meters squared.

treatment group, age, sex, race, diabetic status, weight at implantation, and site as predictors.

The primary safety objective was analyzed using a 1-sided exact binomial test at the 0.025 significance level. Superiority of the mean percentage of excess weight lost was compared between groups using a 1-sided *t* test at the 0.025 significance level with a 10-point superiority margin. Post hoc testing with a 2-sided *t* test was used to compare weight loss between groups with no superiority margin. In addition, the odds ratio comparing the percentage of excess weight loss thresholds by treatment group are presented as post hoc exploratory analyses. Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc).

## Results

### Baseline Characteristics

The screening and randomization procedure is summarized in Figure 1. Of the 239 participants, 162 were randomized from May 16 to December 27, 2011, to receive the vagal nerve block and 77 to receive the sham device. Twelve-month visits were completed by January 4, 2013. Participant characteristics at baseline are summarized in Table 1.

### Participant Disposition

Seven participants did not receive the implants as randomized. One participant randomized to the sham control group

changed his/her mind immediately before the procedure and withdrew. Another participant in the sham group was anesthetized in the operating room, but because no sham kits were available, an active device was implanted. Five participants in the vagal nerve block group did not receive the implant due to intraoperative exclusions (ie, hiatal hernia >5 cm, previous Nissen fundoplication, food in stomach, cirrhosis or hepatitis C, and inability to locate anterior vagal nerve) and were withdrawn.

Following implantation, 6 patients in the sham group withdrew (3 for patient decision, 3 for adverse events) as did 3 patients in the vagal nerve block group (2 lost to follow-up, 1 for an adverse event). The completion rate of the 12-month visit was 91% in the vagal nerve block group and 86% in the sham control group.

During the 12-month blinded study period, 8 patients (4.9%) in the vagal nerve block group had undergone a revision procedure to reposition or replace the neuroregulator; no revisions were required in the sham group. Five participants (3.1%) in the vagal nerve block group and 8 (10.4%) in the sham group had the device removed by 12 months. Two patients in the vagal nerve block did so because 1 had experienced pain at the neuroregulator site and the other, heartburn. Of the 4 patients in the sham group, 1 had pain at the neuroregulator site, 1 needed to undergo magnetic resonance imaging to investigate causes for shoulder pain, 1 had worsening of irritable bowel syndrome symptoms, and 1 had breast cancer. Three patients in the vagal nerve block group and 4 in the sham group asked to have the devices removed.

### Efficacy

At 12 months in the ITT population (Table 2), the mean percentages of excess weight loss was 24.4% in the vagal nerve block group and 15.9% in the sham group with a mean difference of 8.5 percentage points (95% CI, 3.1-13.9). This difference did not meet the primary efficacy objective of achieving superiority with a 10 percentage-point margin ( $P=.71$ ), although weight loss was statistically greater in the vagal nerve block group ( $P=.002$  for treatment difference in post hoc testing). When analyzed using multiple imputation analysis, the mean percentage of excess weight loss was 26.1% in the vagal nerve block group and 16.9% in the sham group with a mean difference of 9.2 percentage points (95% CI, 2.7-15.6). Figure 2 illustrates the percentage of excess weight loss as observed through 12 months. The mean percentage of initial body weight loss at 12 months in the ITT population was 9.2% in the vagal nerve block group and 6.0% in the sham group for a mean difference of 3.2 percentage points (95% CI, 1.1-5.2).

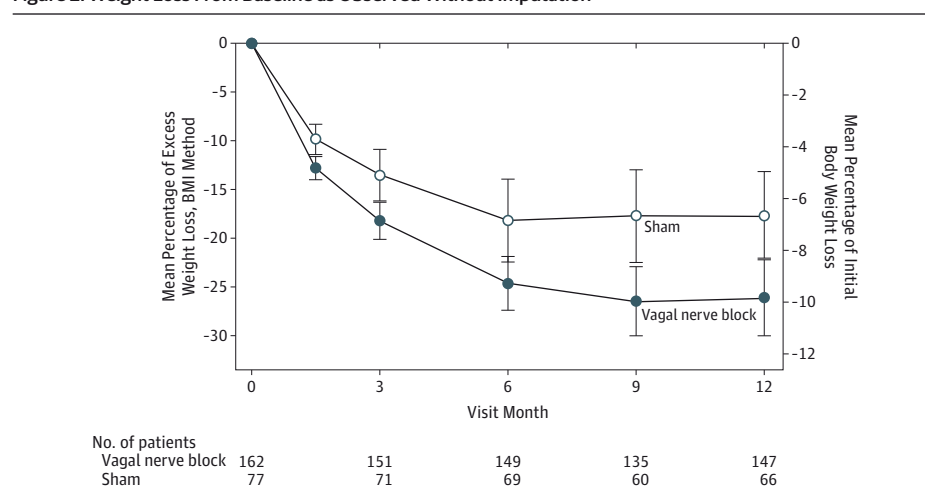
At 12 months, 52% of participants in the vagal nerve block group achieved at least 20%; and 38%, at least 25% of excess weight loss (Table 2), which did not meet the primary efficacy objective performance goals of at least 55% of participants achieving a 20% excess weight loss and 45% achieving a 25% excess weight loss. Table 2 presents the percentage of participants reaching weight loss thresholds from 20% to 50% as well as the post hoc exploratory odds ratios showing higher odds of participants in the vagal nerve block group achieving those thresholds than participants in the sham group.

Table 2. Twelve-Month Percentage Excess Weight Loss

	Mean (95% CI)		Difference (95% CI)
	Vagal Nerve Block (n=162)	Sham (n=77)	
Continuous outcomes			
Percentage of excess weight loss			
LOCF	24.4 (20.8-28.1)	15.9 (11.9-19.9)	8.5 (3.1-13.9)
Multiple Imputation	26.1 (22.2-29.9)	16.9 (11.6-22.2)	9.2 (2.7-15.6)
Categorical Outcomes			
	No. (%) of Patients		Odds Ratio (95% CI)
Percentage of excess weight loss threshold, LOCF			
20	85 (52)	25 (32)	2.3 (1.3-4.1)
25	62 (38)	18 (23)	2.0 (1.1-3.8)
30	49 (30)	14 (18)	2.0 (1.0-3.8)
35	42 (26)	7 (9)	3.5 (1.5-8.2)
40	35 (22)	4 (5)	5.0 (1.7-14.7)
45	30 (19)	3 (4)	5.6 (1.7-19.0)
50	24 (15)	1 (1)	13.2 (1.8-99.6)

Abbreviation: LOCF, last observation carried forward.

Figure 2. Weight Loss From Baseline as Observed Without Imputation



Error bars indicate 95% CIs. BMI indicates body mass index.

## Safety

The primary safety end point, the rate of serious adverse events that were related directly to the device, implantation or revision, or therapy in the vagal nerve block group, was 3.7% (95% CI, 1.4%-7.9%); therefore, the primary safety objective was met ( $P < .001$ ). Two serious adverse events were for neuroregulator malfunction requiring replacement and 1 was pain at the neuroregulator site following a large weight loss (80% of excess weight loss), which required repositioning; these participants were hospitalized overnight and discharged. One participant developed atelectasis, which prolonged hospitalization by 2 days. One patient developed emesis and needed a hiatus hernia repair and was discharged 2 days following repair. One participant had gallbladder disease, which was determined to be possibly related to therapy due to weight loss.

Nine serious adverse events were related to general intra-abdominal surgery. Six were for nausea resulting in prolonged hospitalization of at least 1 day longer than what is typical for the procedure. One was for intraoperative oozing, which resulted in overnight hospitalization and hemodynamic monitoring.

A participant who had not received an implant due to an intraoperative exclusion for cirrhosis was hospitalized because of a complicated liver biopsy. One participant had a moderate ileus of the stomach, was treated with pain medications, and was discharged on the second postoperative day. Combining the serious adverse events that were related to intra-abdominal surgery with those related to vagal nerve block, the rate was 8.6% (95% CI, 4.8% to 14.1%). eTable 1 in Supplement 2 lists all serious adverse events by the adjudicated cause of the event.

The most common adverse events related to treatment are reported in Table 3. Pain at the neuroregulator site was the most common event in both groups. Ninety-six percent of these events in the vagal nerve block group were deemed to be mild or moderate, although a revision was performed in 3 cases and an explant in 1 due to pain. Heartburn and dyspepsia, abdominal pain, other or nonspecific pain, dysphagia, and eructation or belching were reported more frequently by participants in the vagal nerve block group and were attributed by investigators to be primarily related to therapy. All events were



Table 3. Adverse Events Related to Treatment Through 12 Months

Adverse Event	Vagal Nerve Block (n=162)		Sham (n=77)	
	No. (%) Patients	No. Events	No. (%) Patients	No. Events
Pain, neuroregulator site	61 (38)	73	32 (42)	35
Heartburn/dyspepsia	38 (23)	42	3 (4)	3
Pain, other	37 (23)	42	0	0
Pain, abdominal	20 (12)	26	2 (3)	2
Nausea	11 (7)	14	1 (1)	1
Dysphagia	13 (8)	13	0	0
Eructation/belching	13 (8)	13	0	0
Incision pain	12 (7)	13	7 (9)	7
Chest pain	9 (6)	9	2 (3)	2
Cramps, abdominal	7 (4)	7	0	0
Wound redness or irritation	7 (4)	7	5 (6)	5
Appetite increased	5 (3)	6	2 (3)	3
Constipation	6 (4)	6	7 (9)	8
Emesis/vomiting	5 (3)	6	2 (3)	2
Bloating, abdominal	5 (3)	5	1 (1)	2
Headache	5 (3)	5	2 (3)	2

Only adverse events attributed by the investigator to the device, procedure, or therapy that occurred in at least 3% of vagal nerve block group participants are displayed.

adjudicated as mild or moderate in severity, and most were resolved with alteration to the therapy algorithm. Nausea was reported more frequently by participants in the vagal nerve block group, which was expected given that sham implant procedures had no peritoneal penetration. Eighty-six percent of nausea events were mild or moderate.

## Discussion

In this study of patients with morbid obesity, the percentage of excess weight loss among participants treated with vagal block did not meet either of the coprimary efficacy objectives, although weight loss in the intervention group was statistically greater than in the sham group. The vagal nerve block group nearly achieved the 25% mean excess weight loss response predicted in the trial design, but the sham group response was 3 times greater than predicted. Fifty-two percent of participants in the vagal nerve block group achieved 20% and 38% achieved 25% excess weight loss; however, those were lower percentages than the study's objective of 55% achieving a 20% loss and 45% achieving a 25% loss. Weight loss was achieved with a low rate of serious adverse events related to device implantation or function, and most adverse events were mild or moderate in severity.

This is 1 of 3 reported trials testing devices to treat obesity in which a randomized, sham-control method was used.<sup>6-8</sup> To our knowledge, it is the first to report a statistically greater weight loss among treated patients than among those in the control group. Previous trials with an earlier version of the vagal nerve block device<sup>6</sup> and with an implantable gastric stimulator<sup>8</sup> did not produce statistically different treatment effects. Randomized placebo controlled trials have been the standard in obesity trials involving medication and lifestyle intervention, but up to this time, obesity device trials, such as those for laparoscopic adjustable gastric band, have rarely in-

cluded a sham comparator or a 10%-point superiority margin. Consequently, the trial used an unusually strong design to study this obesity-treatment device.

It is likely that the sham group weight loss was due to a placebo effect of surgery, daily self-monitoring reinforced by interaction with the sham device to recharge the battery, and participation in the weight management program. Placebo control groups in recent obesity medication studies have shown 1% to 2% initial body weight loss.<sup>9-11</sup> Lifestyle counseling without medication or meal replacements produced a 3.5% initial body weight loss at 12 months in a controlled trial.<sup>12</sup> The 6% initial body weight loss seen in the sham group in this study is similar to the sham effect in the previous vagal nerve block trial (EMPOWER)<sup>6</sup> and to the control group in the recent SHAPE trial of an implantable gastric stimulator.<sup>8</sup> At the time this trial was designed, weight loss in the previous vagal nerve block sham treatment was thought to be due to inadvertent active treatment. In the EMPOWER study, there was a relationship between hours of use and weight loss, regardless of assignment to active or control groups.<sup>6</sup>

Sham surgeries are known to have substantial placebo effects in other contexts, such as arthroscopic knee surgery,<sup>13,14</sup> vertebroplasty for back pain,<sup>15,16</sup> and internal mammary artery ligation for angina.<sup>17</sup> The sham effect was sufficient in each of these cases to result in a conclusion of ineffectiveness for the intervention. A recent review article highlights the large sham effects observed with surgical interventions.<sup>18</sup> Furthermore, the structure of a clinical weight loss trial imposes more than usual behavioral changes, notably in the form of self-monitoring of behavior and weight, which may have important effects.<sup>19</sup> The results in the ReCharge trial are therefore of heightened interest because the post hoc analysis showed greater weight loss in the active group despite a robust sham effect.

Adverse events in this trial were less severe than those associated with conventional bariatric surgical procedures, pri-

marily mild or moderate events related to therapy. Recent reports of uncontrolled clinical trials and registry data provide comparative safety data on laparoscopic adjustable gastric band.<sup>20-22</sup> Overall, the rate of device-related adverse events in the Helping Evaluate Reduction in Obesity (HERO) registry appears to be 4.7%.<sup>20</sup> Phillips et al<sup>21</sup> reported adverse events that included dysphagia (9.4%), gastroesophageal reflux (19.2%), and vomiting (40.6%) and a reoperation rate of 15.2%. Cobourn et al<sup>20</sup> reported a low rate of band-related complications, but a reoperation rate of 15.2%. Late complications for laparoscopic adjustable gastric band include band slippage and pouch dilation, which occurs in up to 20% of patients, and band erosion occurring in up to 4% of patients.<sup>23</sup> However, adverse events of vagal nerve block have not yet been reported following widespread use. Rates of adverse events often increase when therapies are used in general populations.

This study has limitations including the demographics of the study participants, which were primarily white women, so inference to other groups must be made with care. Further-

more, the study population had a low rate of diabetes, a common comorbidity of significant obesity, and a low rate of other metabolic complications such as hypertension and dyslipidemia. The study focused on obesity in the BMI range of 35 to 45, so application of the treatment to individuals with higher BMI will need careful consideration.

## Conclusions

Among patients with morbid obesity, the use of vagal nerve block therapy compared with a sham control device did not meet either of the coprimary prespecified efficacy objectives, although the intervention group had statistically greater weight loss than the sham control group. The treatment met the primary safety objective and was well tolerated. Additional studies are needed to compare effectiveness of vagal nerve block with other obesity treatments and to assess long-term durability of weight loss and safety.

### ARTICLE INFORMATION

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**Author Contributions:** Drs. Billington and Sarr had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Tooili, Kow, Knudson, Tweden, Shikora, Sarr, Billington.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Miller, Knudson, Tweden, Shikora, Sarr, Billington.

**Critical revision of the manuscript for important intellectual content:** Ikramuddin, Blackstone, A. Brancatisano, Tooili, Wolfe, Fujioka, Maher, Swain, Que, Morton, Leslie, R. Brancatisano, Kow, O'Rourke, Deveney, Takata, Miller, Knudson, Tweden, Shikora, Sarr, Billington.

**Statistical analysis:** Miller.

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**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ikramuddin reported that he serves on the advisory board for Novo Nordisk Inc and Medica; has served as a consultant for Metamodix Inc and on an expert panel for OptumHealth; and has received grant support from USGI Medical Inc, ReShape Medical, and Covidien. Dr Brancatisano reported that he is a consultant for EnteroMedics. Mr Miller reports consulting support from EnteroMedics, Inc. Dr Fujioka reported receiving personal fees from EnteroMedics for help and consulting with European device approval. Dr Swain reports personal fees from surgical proctoring for EnteroMedics. Dr Knudson reported that he is the chief executive officer of EnteroMedics and codeveloped the patented vagal nerve blockade device, which is owned by EnteroMedics. Dr Tweden reported that she is an employee of EnteroMedics and codeveloped the patented vagal nerve blockade device, which is owned by EnteroMedics. Dr Sarr reported that he is a consultant for EnteroMedics. Dr Billington reported that he is a consultant for EnteroMedics and NovoNordisk and has received pgrant support from Covidien.

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participate in the critical revision of the manuscript prior to submission.

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