Early Feasibility Clinical Study of Gastric Electrical Stimulation (GES) for the Treatment of Obesity using the Exilis* System

Published: 27-02-2013
Last updated: 26-04-2024

The study is intended to provide insight into the clinical feasibility of the Exilis* system as a therapy for obesity, including:* Providing initial human safety data on the Exilis* system, * Gaining an understanding of how to individually titrate...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39780

Source
ToetsingOnline

Brief title
Early Feasibility Clinical study of GES

Condition

- Other condition

Synonym
Obesity

Health condition

Obesitas

Research involving

Human

Sponsors and support

Primary sponsor: Medtronic
Source(s) of monetary or material Support: Medtronic Bakken Research Center BV

Intervention

Keyword: Exilis System, Gastric Electrical Stimulation (GES), Obesity

Outcome measures

Primary outcome

1. To obtain first-in-human experience with the Exilis* system, including initial clinical feasibility and safety data, as well as data on device performance (e.g., recharge durations and intervals) and use conditions (e.g., stimulation amplitudes, lead impedances). These data will inform decisions about whether to pursue further clinical studies with the Exilis* system, or whether the Exilis* system or the way it is used should be modified before pursuing further clinical studies.

2. To gain an understanding of what sensations, if any, subjects feel during GES treatment, and what level and type of sensations subjects find acceptable and comfortable during chronic daily treatment. If subjects do report sensations during GES, data collection on these sensations will be used to develop sensory-based programming procedures for the Exilis* system to aid identifying the highest comfortable pulse amplitude for chronic treatment during a single brief clinic visit.

Secondary outcome

1. To determine whether GES delivered with the Exilis* system delays gastric

emptying, and whether any GES-induced delay in emptying persists under prolonged chronic daily treatment. Medtronic*s preclinical research has found that GES like that delivered by the Exilis* system delay gastric emptying in rodents, canines and swine, and that a larger GES-induced delay in gastric emptying in rodents correlates with a larger GES-induced reduction in feeding. Delayed gastric emptying has been linked to early and prolonged satiation in both humans and animals , and is suspected to be part of the mechanism of action by which the Exilis *GES system may reduce food intake and body weight. Thus an objective of the study is to confirm whether GES-induced delays in gastric emptying observed in animal models can be replicated in humans.

2. To determine whether GES delivered with the Exilis *system suppresses post-meal gastric contractile activity. Medtronic*s preclinical research has included numerous measurements of gastric contractile activity in canines following the ingestion of a solid meal. These tests have repeatedly shown that GES treatments like that delivered by the Exilis* system suppress post-meal gastric contractile activity that occurs during the processing of a meal into chyme before it passes into the small intestine. This effect is at least part of the mechanism by which GES delays gastric emptying. In canines this post-meal motility suppression effect of GES has been measured using a manometric catheter placed in the gastric antrum, and observed directly via fluoroscopy following a barium-labeled test meal. In the proposed study, gastric contractile activity will be monitored noninvasively using a SmartPill gastrointestinal pressure, pH and temperature monitoring device that will be ingested with water by the subject just prior to consumption of the breakfast

test meal.

3. To determine whether GES delivered with the Exilis* system reduces post-meal plasma glucose and insulin concentrations. Delaying gastric emptying slows the rate at which ingested nutrients are absorbed into the bloodstream, blunting the rise in blood glucose and insulin levels following a meal. This effect may be beneficial in reducing episodes of postprandial hyperglycemia that are associated with an increased risk of mortality from cardiovascular diseases. Medtronic*s preclinical research has found that delivery of the Exilis* GES signal reduces postprandial glycemic levels in both diabetic and obese non-diabetic rats. Measurement of the post-meal profiles of plasma glucose and insulin during gastric emptying tests conducted with GES On and GES Off during the study will provide a test of whether the postprandial glycemic control effects of GES observed in rats can be duplicated in humans. Further assays of the blood samples collected in conjunction with the gastric emptying test meals may also be analyzed to explore whether GES similarly alters plasma levels of gut peptides involved in regulating food intake and body weight, including GLP-1, PP, PYY, CCK, ghrelin and leptin.

4. To determine whether GES delivered with the Exilis* system reduces caloric intake during a standardized ad libitum solid meal consumed in a controlled setting. Medtronic preclinical research has found that GES treatments like that delivered by the Exilis* system reduce food intake in rodent, canine and swine models. Meal pattern analysis in rodents with 24 hour ad libitum food access found that GES-induced reductions in food intake were due to reduced meal size, with the number and timing of daily meals being unaltered. Caloric intake will

be measured in study subjects during an ad libitum lunch test meal consumed in a controlled setting on two occasions*once with GES On and once with GES Off* will be used to test whether the GES-induced reduction in meal size observed in animals can be replicated in humans.

5. To characterize data on any changes in other physiological parameters, medication usage, and psychometric assessment scores that occur during chronic daily GES treatment with the Exilis* system. Physiological parameters of interest for this objective include body weight, waist and hip measurements, pulse rate, blood pressure, blood lipids, fasting blood glucose, HbA1c levels and reported levels of physical activity, as measured by International Physical Activity questionnaire (IPAQ). Psychometric assessments will include general (SF-12) and obesity-specific (IWQoL-Lite) quality of life instruments, the Three Factor Eating Questionnaire (TFEQ), and visual analog scale ratings of hunger and fullness.

Study description

Background summary

The prevalence of obesity is rising worldwide, and the majority of adults in the United States and many developed countries are overweight or obese. It is estimated that 1.5 billion adults worldwide are overweight (BMI>25) and 500 million are obese (BMI *30)1. The increasing prevalence of obesity in the US has been accompanied by an even more rapid rise in the prevalence of severe obesity (Class II and III, BMI *35)2. Rates of severe obesity among US adults more than tripled between 1986 and 2000, and by 2008 an estimated 33 million US adults or 14.3% of the adult population were severely obese.
Obesity is associated with higher rates of disability and all-cause mortality, and the obese have increased incidences of type II diabetes, cardiovascular disease, musculoskeletal disorders, sleep apnea, fatty liver disease and certain cancers4. Obesity and its co-morbidities are estimated to claim more

than 100,000 lives5 and add $147 billion to health care costs annually in the US alone6. The health consequences of obesity increase with BMI, concentrating most of the disease and cost burden of obesity among the severely obese. Severely obese adults have all-cause mortality rates nearly twice as high as normal weight individuals7, and are 5.5 times as likely to have type II diabetes, three times more likely to require anti-hypertensive medications, and 1.7 times more likely to be diagnosed with heart disease8. While annual health care expenditures for US adults with Class I obesity (30* BMI<35) have been estimated to be 25% greater than for normal weight adults, this excess in health care cost over normal weight adults doubles to 50% for adults with Class II obesity (35*BMI<40), and quadruples to 100% for the Class III obese (BMI*40)9.

Even though many severely obese patients achieve weight loss through behavioral treatments focused on diet and exercise, only a small minority of these patients succeed in maintaining their losses. As a result, the expected weight loss efficacy of these interventions declines to near zero within five years from the start of treatment.
Available pharmacotherapy options for obesity are limited. The lipase inhibitor orlistat is currently the only anti-obesity drug approved for long term use in the US. This agent has, at best, modest efficacy that is only sustained as long as patients continue taking the drug. More than 90% of patients who try orlistat cease taking it within one year. This rapid attrition in usage, which is in part driven by the adverse gastrointestinal side effects of the drug, makes the expected long term efficacy orlistat minimal. At present, prospects for more effective new pharmacotherapies appear poor. Recent years have seen several candidate anti-obesity drugs fail to obtain regulatory approval due to inadequate efficacy, adverse side effects, or both.
The only treatments for severe obesity that have demonstrated sustained long term efficacy are bariatric surgeries, with the two dominant procedures being adjustable gastric banding (AGB) and Roux-en-Y gastric bypass (RYGB). These two procedures account for over 80% of the more than 350,000 bariatric surgeries performed annually worldwide. In a recent systematic review of weight loss outcomes in comparative studies of these procedures, AGB and RYGB patients lost averages of 31-55% and 51-76% of their excess body weight at one year, respectively. These weight losses were accompanied by resolution of type II diabetes in 40-77% and 72-100% of diabetic AGB and RYGB patients, and resolution of hypertension in 27-70% and 61-81% of hypertensive AGB and RYGB patients at one year post-surgery. In the longer term, both AGB and RYGB patients regain, on average, a portion of their maximal weight loss, with this regain tending to be greater in the case of AGB. Long term follow-up of a large cohort of bariatric surgery patients in the Swedish Obese Subjects study, however, found that gastric banding and bypass patients maintained an average of 68% and 77% of their one-year weight loss a decade after surgery, and that this degree of sustained weight loss was sufficient to significantly reduce their all-cause mortality relative to matched controls who did not undergo bariatric surgery.

Compared to other widely used medical interventions, bariatric surgery has been found to be a cost-effective means of extending longevity and improving quality of life, and there is some evidence that the costs of bariatric surgery are more than fully offset by the reductions in future medical costs associated with the resolution or improvement of obesity-related comorbid conditions. Despite growing evidence of the benefits of bariatric surgery and a rapid rise in procedure volumes over the past two decades, only a small percentage of obese patients who are candidates for bariatric surgery under the standard criteria*(BMI *40, or 35* BMI <40 with an obesity-related comorbidity)*will ever undergo bariatric surgery17. A likely reason for this is that patient acceptance is limited by the of 10-20% rates of serious complications reported for AGB and RYGB surgeries, the potential for permanent adverse side effects (e.g., chronic vomiting, GERD, dumping syndrome, nutrient deficiencies), and the fact that the alterations in anatomy associated with these procedures are difficult or impossible to reverse in response to a poor outcome.

Study objective

The study is intended to provide insight into the clinical feasibility of the Exilis* system as a therapy for obesity, including:
* Providing initial human safety data on the Exilis* system,
* Gaining an understanding of how to individually titrate stimulation amplitude to a level that subjects will find comfortable under chronic daily treatment,
* Collecting data on acute gastrointestinal (GI) and feeding responses to GES to confirm whether effects of GES observed in animal models can be replicated in human subjects, and
* Characterize changes in physiologic parameters (e.g. weight, blood pressure) with GES

Study design

Up to 20 obese (BMI 35-45) subjects, aged 21-64, will be implanted with the Exilis* system in this study at up to three clinical sites in Europe and the United States. Chronic daily GES treatment will be delivered in the context of a single arm study design, with all subjects receiving active GES, 16 hours per day, during waking hours. The chronic daily GES treatment settings will be determined by a series of amplitude titration assessments. Data will be collected at regular clinic visits for up to five years or more from implant.
All subjects will receive a Health and Wellness program consisting of six In Person visits with a dietitian and 15 on-line educational lessons.
Study subjects will also complete a suite of gastrointestinal (GI) function tests, and a solid meal satiety test. The tests will be repeated twice during a pair of 6-7 hour clinic visits following the first month of daily GES treatment as part of an acute response cross-over experiment. GES will be On during one of these testing visits and Off during the other, in a randomly assigned order, with subjects blinded to test day treatment assignments. Apart from during

these two visits, subjects as well as clinicians will be unblinded with respect to GES delivery throughout the study. Each of these testing visits will be preceded by a washout period, approximately one week in duration, during which subjects will receive no GES treatment. As detailed in Section 6 of this protocol, with the proposed sample size of 20 implanted subjects, this acute cross-over experiment component of the study has ample statistical power to detect clinically significant changes in gastric motility and solid meal satiety test caloric intake across GES Off and GES On treatment days. Duration between test visits will vary with those participating in the substudy.

Intervention

The medical intervention consists of the implantion of the exilis system using a laprorascopic surgical procedure. Placement of two electrodes near the pylorus and the remaining of the system in the abdominal area closely under the skin.

Study burden and risks

The potential risks have been classified according to if the potential risk is related to the Procedure, Device, or Therapy. The following are the identified potential risks associated with the Exilis System and its intended use. There may be additional risks related to study participation that are unknown at this time.
There are procedural-related risks associated with the laparoscopic surgery, including death. The risks associated with this surgery are risks that can occur with other laparoscopic surgeries. Some of these risks, such as the risks of general anesthesia, are increased for a person who is obese.

Subjects may benefit from their participation in the study through weight loss and an improvement in its associated comorbidities and/or quality of life indices.
Indirect benefits include: the knowledge that the subject is contributing to a better understanding of the use of GES for Obesity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject is 21-64 years of age inclusive at time of screening;
2. Subject is willing to sign and date an informed consent and a data privacy authorization for their Participation;
3. Subject has a BMI of 40-45 kg/m 2 or 35-39.9 kg/m2 with at least one weight-related comorbidity diagnosed prior to screening; (e.g. , obstructive sleep apnea, nonalcoholic steatohepatitis, hypertension, dyslipidemia, gastroesophageal reflux disease, asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis);
4. If subject is diagnosed with diabetes mellitus, must be Type 2 diabetes diagnosed within the last 7 years, currently treated with diet, exercise and /or oral agents only, and with a HbA1c of *8% without significant complications due to their diabetes in the judgment of the principal investigator;
5. Subject must be an acceptable candidate for laparoscopic implant under general anesthesia of the Exilis* system in the opinion a qualified surgeon performing the implant and can anatomically accommodate all implanted hardware which includes the ability to palpate the rib cage at the intended ICC implant location;
6. Subject reports failure at prior weight loss attempts using non-surgical approaches;
7. Subject reports their weight as being within 5% of their current body weight for at least one year;
8. Subject must, if female, be at least two years post-menopausal (defined as two years without menses), or surgically sterile (must be documented), or must agree to the use of effective contraception (devices, oral or implanted) for the duration they are enrolled in the

study;
9. Subject must, if female, be non-lactating, and if of child-bearing potential, have a negative serum pregnancy test result prior to implant;
10. Subject must speak and understand English or Dutch with sufficient proficiency to read, comprehend, and sign the informed consent document and privacy statement, and to communicate with study staff;
11. Subject must have regular access to the internet running one of the following browsers: Internet Explorer 8+, Firefox 3+, Safari 4+, or Google chrome;
12. Subject reports having regular sleeping hours that do not frequently vary due to night shift worker regular long distance travel across four or more time zones;
13. Subject is willing to comply with daily recharging of device up to 90 minutes daily;
14. Subject is willing to fast overnight with no food, water only, for up to 12 hours;
15. Subject is willing to swallow a large rounded pill capsule, approximately 1.3 cm in diameter
16. Subject is willing to complete all scheduled study visits and procedures as defined in the Informed Consent;

Exclusion criteria

1. Subject has a history of medical, surgical, or psychiatric conditions that, in the opinion of the Investigator, would limit study participation;
2. Subject has presence of untreated or inadequately treated DMS-IV AXIS I (or greater) disorder and/or significant problematic eating behaviors that could interfere with long-term goals; unrealistic expectations or surgical results; might lack social support, understanding of surgery or have ineffective coping mechanism, upon completion of psychological analysis.
3. Subject has evidence of clinically significant ECG abnormalities, in the opinion of the Investigator at the Screening Visit;
4. Subject is currently taking, or has taken in the past 3 months, any prescription or over-the-counter medications that, in the Investigator's opinion could interfere with the subject*s suitability for participation in the study, including in particular any medications taken for the purpose of weight loss or that have been shown to affect GI motility;
5. Subject has been diagnosed with an eating disorder within the past five years;
6. Subject had prior GI surgery (e.g. bariatric surgery, fundoplication, gastric resection or major upper abdominal surgery);
7. Subject has a history of inflammatory disease (e.g. Crohn*s disease or ulcerative colitis) of the GI tract;
8. Subject has a history of functional and/or motility disease (e.g., gastroparesis) of the GI tract;
9. Subject has a history of pulmonary embolism or blood coagulation disorders;
10. Subject has a history of gastric bezoar, diverticulitis, disorders of swallowing, dysphagia to food or pills, suspected strictures, fistulas, or physiological obstruction in the GI tract;
11. Subject has an allergy or sensitivity to wheat, egg, soy, milk, tree nuts, or orange juice, all of which my be contained in the test meals consumed for the study gastric emptying or solid meal satiety tests;
12. Subject has a known genetic cause of obesity (e.g., Prader-Willi Syndrome);

13. Subject currently has active implantable medical devices or wears external stimulation and/or drug delivery medical devices;
14. Subject reports anticipating undergoing an MRI examination during the study duration; or subject reports anticipating undergoing diathermy (shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy) during the study duration;
15. Subject is currently participating in any investigational drug, device or biologic study; and
16. Subject has a history of heart disease (e.g. angina, history of myocardial infarction, previously documented arrhythmia) that may increase the risk of sudden cardiac death, in the opinion of the Investigator.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-02-2013
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	Exilis system
Registration:	No

Ethics review

Approved WMO

Date:	27-02-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	29-07-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-02-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-03-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL41872.068.12
Other	www.ClinicalTrails.gov