Title: Hybrid Argon Plasma Coagulation and Endoscopic Sleeve Gastroplasty Trial (HAPCET): A Single-Center Randomized Control Trial

NCT Number: NCT05559866

Document Date: 09/24/2024

Hybrid Argon Plasma Coagulation and Endoscopic Sleeve Gastroplasty Trial (HAPCET): A Single-Center Randomized Control Trial

Principal Investigator **Omar Ghanem, MD**
Surgery – Metabolic Surgery
200 1st St SW, Rochester, MN 55905
507-266-4347

Site Investigators **Omar Ghanem, MD**
Associate Professor of Surgery, Mayo Clinic

Jeff L. Fidler, M.D.
Professor of Radiology, Mayo Clinic

Legal Sponsor **Mayo Clinic**
201 1st St SW
Rochester, Minnesota 55902
507-284-2511

Funding Partner: **Erbe USA, Incorporated**
2225 Northwest Parkway
Marietta, Georgia 30067
770-955-4400

Erbe Elektromedizin GmbH
Waldhörnlestr. 17 · 72072 Tübingen, Deutschland
+49 7071 7550

Study Product: Hybrid Argon Plasma Coagulation (HAPC)

System Accounts:

IRBe 22-001202
PLM 2022-307124-H01

Contents

Protocol Signature Page

Study Title: HYBRID ARGON PLASMA COAGULATION AND ENDOSCOPIC SLEEVE GASTROPLASTY TRIAL (HAPCET): A SINGLE-CENTER RANDOMIZED CONTROLLED TRIAL

Protocol Version Number: Version 2

Protocol Date: 10AUG2022

Sponsor: Mayo Clinic, Rochester, MN

The undersigned have read and understand the Protocol specified above and agree on its content. I agree to conduct the study according to this protocol, its amendments, the clinical trial agreement and the applicable regulatory requirements. I understand that said study will not be initiated without appropriate Institutional Review Board (IRB) approval and that the administrative requirements of the governing body will be fully complied with.

_____	_____
Principal Investigator's Printed Name and Signature	Date
_____	_____
Site Name	Site Number

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ANCOVA	Analysis of covariance
APC	Argon Plasma Coagulation
APMC	Argon Plasma Mucosal Coagulation
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CO2	Carbon dioxide
COPD	Chronic Obstructive Pulmonary Disease
CPE	Complete Physical Exam
CRF	Case Report Form
DSMP	Data safety monitoring plan
DRAE	Device-Related Adverse Event
DVT	Deep Vein Thrombosis
eCRF	Electronic case report form
EDC	Electronic Data Capture
EGD	Upper endoscopy/esophagogastroduodenoscopy
EKG	Electrocardiogram
EMR	Electronic medical record
ESG	Endoscopic Sleeve Gastroplasty
EWL	Excess Weight Loss
GE	Gastric Emptying
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GLP-1	Glucagon-like peptide
HAPC	Hybrid Argon Plasma Coagulation
HDL	High-Density Lipoprotein
ICF	Informed Consent Form
ICU	Intensive Care Unit
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IWQOL-lite	Impact of Weight on Quality of Life - Lite
LDL	Low-Density Lipoprotein
MAR	Missing at random
mITT	Modified intent-to-treat
MRI	Magnetic Resonance Imaging
NAFLD	Non-Alcoholic Fatty Liver Disease
NES	Night Eating Syndrome
NPO	Nothing by mouth
NSAID	Non-steroidal anti-inflammatory drug
PCP	Primary Care Provider
PE	Pulmonary Embolism
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
PTT	Partial Thromboplastin Time
RGYB	Roux-En-Y Gastric Bypass
SAE	Serious Adverse Event/Serious Adverse Experience

SCD	Sequential Compression Device
SGOT/AST	Serum Glutamic-Oxaloacetic Transaminase /Aspartate Aminotransferase
SGPT/ALT	Serum Glutamic-Pyruvic Transaminase /Alanine Aminotransferase
SDRAE	Serious Device-Related Adverse Event
SF-36	Short Form Health Survey
TBWL	Total Body Weight Loss
TFEQ	Three-Factor Eating Questionnaire
TORe	Transoral outlet reduction
UADE	Unanticipated Adverse Device Effects

1. ABSTRACT

The obesity epidemic continues to grow in the United States with the prevalence of obesity increasing up to nearly 43% in 2019 with current projections estimating one in every two US Adults by 2030.[1, 2] Obesity is associated with type 2 diabetes, coronary artery disease, chronic joint disease, obstructive sleep apnea, nonalcoholic fatty liver disease (NAFLD), and malignancy. Obesity is associated with an increased risk of all-cause and cardiovascular mortality and accounts for about 2.5 million preventable deaths annually. [3-5] Obesity treatment is limited as lifestyle modifications provide only a modest total body weight loss with a high rate of weight recidivism.[6] Widely available medical therapies are plagued by intolerance, cost, attenuated response, and weight regain after cessation of pharmacotherapy[7]. Newer GLP-1 analogues while providing significant weight loss require further investigation to determine if the weight loss effect is durable long term.[8-11] Bariatric surgical interventions have been associated with significant side effects, micronutrient deficiencies and weight regain, however they have proven to be the most durable and effective[12]. Unfortunately, they are usually unavailable to patients with Class 1 to Class 2 obesity (BMI 30-40 kg/m)[13]. This has led to a significant management gap for patients with mild to moderate obesity. Endoscopic sleeve gastroplasty (ESG) is an endoscopic, minimally invasive intervention that has demonstrated clinically significant, sustained, weight loss ranging between 15-19%.[14] However, given lack of approximation of submucosal structures with ESG to enhance wound healing and fibrogen deposits at the gastroplasty construct, durability of the gastroplasty construct is not maximized[15]. We have shown enhanced durability of ESG when combining it with endoscopic submucosal resection techniques[16]. However, this is technically challenging and only allows treatment in the distal stomach. Argon plasma coagulation is effective in the transoral outlet reduction (TORe) procedure to help reduce the gastric outlet aperture in patients with weight regain after bariatric surgery by creating a focal coagulation injury in a circumferential manner that ablates the mucosal layer and aids in wound healing[17]. One case report evaluation using APC at time of ESG which demonstrated enhanced fibrosis at the site of endoscopically placed sutures potentially improving the durability and of the ESG and reducing complications of more invasive mucosal ablation methods such as endoscopic submucosal dissection or endoscopic mucosal resection techniques.[18] Furthermore, APC application is technically easy with scalable skill-set to the average endoscopist[19]. Hybrid APC (HAPC) with submucosal lift offers enhanced safety; especially in ablating the mucosa in the proximal stomach, where the gastric wall is thin, to minimize risk of deep gastric wall injury. While this is hybrid approach is promising, controlled proof of concept evidence is required. Therefore, we propose a pilot randomized control trial evaluating the safety, durability of ESG in combination with HAPC and its effect on weight loss compared against traditional ESG alone in patients with obesity and body mass index (BMI) between 30-40 kg/m2.

2. INTRODUCTION

Background

The obesity epidemic continues to grow unabated in the United States[20]. The prevalence of obesity has increased from 30.5% to 42.4% with the prevalence of severe obesity increasing from 4.7% to 9.2% from the year 2000 until 2019 and continues to rise.[1] Currently projections show about one in two United States (US) adults will have obesity, with one in four afflicted by severe disease by 2030.[2] Obesity has significant implications on public health as it is associated with type 2 diabetes, coronary artery disease, chronic joint disease, obstructive sleep apnea, nonalcoholic fatty liver disease (NAFLD), and malignancy. Obesity is associated with an increased risk of all-cause and cardiovascular mortality and accounts for about 2.5 million preventable deaths annually. [3-5] Furthermore, the worldwide economic impact of obesity has been estimated to be $2.0 trillion USD or 2.8% of the global gross domestic product (GDP) and continues to rise.[21]

This problem of obesity is compounded by a lack of sufficient therapeutics. Currently patients with obesity are treated with a combination of lifestyle modifications, medication therapy and in certain instances surgical intervention. While lifestyle modification remains the foundation for successful obesity management, alone it yields only about a 3% total body weight loss.[22-24] Furthermore weight regain is a problem with lifestyle modifications[25]. Studies have shown that 1 year following dietary and lifestyle modification therapy, 20%-25% of patient's have weight regain. This number swells to more than 50% at 5 years.[6] The development of GLP 1 agonists used alone or in conjunction with other medications such as amylin analogues has shown promise for treatment of obesity as these medications produced between 8% and 16% with a favorable side effect profile.[8-11] However, there are no long terms studies evaluating weight regain after cessation of these medications[26]. Prior generations of obesity pharmacotherapy were plagued by intolerance, cost, attenuated response, and weight regain after cessation of the pharmacotherapy[27].

Bariatric surgical interventions are the most effective and durable therapies for management of obesity[28]. However they are limited by invasiveness, expense, long-term risks, and patients' acceptance.[29] Moreover, in younger patients, desire for bariatric surgery is quelled by concerns regarding long-term nutrient deficiencies and need for invasive revisions[30]. Bariatric surgery is only available to about one percent of eligible patients and is not considered for the majority of patients with class I and II obesity without comorbid conditions.[31]

The current obesity management paradigm involves an intervention to provide a robust initial weight loss followed by lifelong engagement of the patient in continued lifestyle modifications[32]. With the weight recidivism seen with obesity pharmacotherapy, and limited availability and cost of bariatric surgical interventions, this has led to the development of endoscopic bariatric therapies to address this gap in treatment[33]. Intragastric balloons have shown promise in inducing weight loss, however intolerance is an issue as side effects such as nausea, vomiting, abdominal pain are commonly seen.[34] Furthermore, more serious side effects such as gastric ulceration, gastric perforation and pancreatitis are recognized side effects.[34-36] Also the limited dwelling time of these intragastric balloons leads to weight recidivism and the need for combination therapies to help ensure continued weight loss[37].

Since it was first demonstrated as a feasible therapy in humans in 2013, the most commonly performed endoscopic bariatric therapy has been the endoscopic sleeve gastroplasty (ESG).[38] This is a minimally invasive endoscopic technique that involves creation of full-thickness plications of the stomach using endoscopic suturing creating a tubular shape to the stomach limiting gastric volume and accommodation similar shape created with surgical sleeve gastrectomy.[39] Multiple studies have shown up to 15% to 18% TBWL with sustenance of this weight loss up to 24 months.[14] Furthermore, studies have demonstrated physiologic perturbations resulting from creation of the ESG and its association with increased satiation and metabolic effects that are important to control the metabolic dysregulation associated with obesity.[40] The ESG procedure is associated with fewer complications than bariatric surgical procedures.[41] However, complications of the ESG procedure include pain, nausea, upper gastrointestinal bleeding, gastric ulceration, and peri-gastric leak or fluid collection.[14] Suture dehiscence and enlargement of the stomach within months requiring revisional procedures have also been seen.[18] Revision is usually performed using a combination of endoscopic suturing as well as argon plasma coagulation[42].

Argon plasma coagulation (APC) is a method of non-contact thermal hemostasis initially created to assist in inducing hemostasis[43]. APC utilizes high-frequency current which applied to the target tissue through an argon plasma jet inducing hemostasis and a homogenous surface coagulation with a limited depth of penetration. This technology has also been used in bariatric endoscopy for patients requiring revision after bariatric surgical procedure[44]. Endoscopic transoral outlet reduction (TORe) is a commonly performed procedure to help manage weight regain after bariatric surgical intervention[45]. The two most commonly performed techniques for TORe are full-thickness suturing with plus argon plasma mucosal coagulation (ft-TORe) and argon plasma mucosal coagulation alone (APMC-TORe). Both of these techniques utilize APC creates a focal coagulation injury in a circumferential manner causing edema, ulceration and fibrosis reducing the aperture of the gastrojejunal anastomosis.[46, 47] This causes a physical reduction in the size of the stoma as well as a delay in gastric emptying[48]. One study showed a reduction in the diameter of the gastrojejunal anastomosis of 67% with approximately 15kg weight loss with APC in patients with weight regain after RGYB.[49] While APC is a useful tool in patients with weight regain following bariatric surgical procedure, it can be combined with ESG to provide enhanced fibrosis along the gastric plications.[18]

Clinical Data to Date

ESG was proven to be feasible in human subjects in 2013 and since then it has become the most commonly performed endoscopic bariatric procedure.[38] Multiple studies have demonstrated significant and sustained weight loss. However, the durability of the plication construct could be enhanced with addition of HAPC. One case report combined the use of ESG and APC and found to have enhanced fibrosis along the site of endoscopic plications potentially providing an avenue for longer and more durable ESG while minimizing these associated complications. Furthermore, with enhanced fibrosis this could decrease the incidence of weight regain in patients undergoing ESG and capitalize on the metabolic benefits of gastric mucosal revitalization reported with APC alone. However, to date no prospective controlled studies have been done comparing traditional ESG to a hybrid ESG and APC procedure.

Rationale

ESG is a commonly performed procedure that has been shown to demonstrate significant weight loss. However, combining it with HAPC technique to enable approximation of submucosal surfaces for enhanced gastroplasty healing, durability of this procedure could be enhanced. This could help maximize the metabolic benefits of gastric mucosal revitalization in conjunction with the restrictive effects of ESG for enhanced weight loss, durability, and metabolic benefits of the combined procedure while minimizing the risk of weight recurrence previously reported with the traditional ESG.

STUDY OBJECTIVES

Assess the safety and durability of combined HAPC and ESG compared to traditional ESG

Assess weight loss and improvement in obesity related co-morbidities in combined HAPC and ESG compared to ESG alone.

STUDY DESIGN

General Description

This is a single-center, randomized, single-blinded clinical trial evaluating the efficacy and safety of combined HAPC and ESG for weight loss and improvement in obesity-related co-morbidities compared to ESG alone in participants with a BMI ≥ 30 and ≤40 kg/m² who have failed to achieve and maintain weight loss with a non-surgical management.

Participants will be recruited from outpatient clinical weight loss clinics and from study-related institutional review board (IRB) approved advertisements.

Twenty-four eligible participants will be block-randomized 1 to 1 treatment (12 participants) and control (12 participants) groups. All participants will undergo endoscopy and those without endoscopic contraindications will be eligible. All treatment group subjects will undergo combined HAPC and ESG where APC is applied according to on-label use prior to the standard ESG technique for enhanced fibrosis along the site of the plications potentially providing an avenue for longer and more durable ESG while minimizing the associated complications. Control subjects will undergo traditional ESG alone. All participants will undergo a repeat upper endoscopy at 26 weeks (6 months) +/- 2 weeks to evaluate the durability of the endoscopic sutures. All subjects will undergo research MRI at baseline and 26 weeks +/- 2 weeks to evaluate and grade the durability of the created gastroplasty, gastric motility, and gastric accommodation. This specially developed MRI protocol at Mayo offers a gold standard in evaluating gastroplasty durability. Additionally, at both baseline and 26 weeks +/- 2 weeks, all patients will undergo gastric scintigraphy to evaluate and measure gastric emptying.

Endpoints
Effectiveness

Primary:

- Assess durability of endoscopic plications and sutures 26 weeks (6 months) +/- 2 weeks post procedure between patients receiving HAPC/ ESG vs traditional ESG alone.

Secondary:

- %TBWL in the combined HAPC and ESG group compared to traditional ESG at 6 and 12 months.
- Assess the procedure safety.
- % Excess weight loss (EWL) at 6 and 12 months between both groups.
- Proportion with ≥25% EWL at 6 and 12 months by randomized arm.
- % of patients in the combined HAPC and ESG group achieving ≥ 5% TBWL at 6 and 12 months compared to ESG alone.
- % of patients in the combined HAPC and ESG group achieving ≥ 10% TBWL at 6 and 12 months compared to ESG alone.
- Changes in quality of life assessed using standard validated questionnaires (IWQOL-lite and SF-36) at 6 and 12 months compared to baseline.
- Changes in depression assessed using PHQ-9 questionnaire at 6 and 12 months compared to baseline.

- Improvement/reduction of hunger and desire to eat evaluated using validated self-reported ratings of appetite based on a 100-mm visual-analogue scale at 6 and 12 months compared to baseline.
- Improvement in eating behaviors evaluated using the Three Factor Eating Questionnaire (TFEQ) at 6 and 12 months compared to baseline.
- Improvement in obesity related comorbidities (blood pressure, fasting glucose, Hba1c, lipid panel, liver enzymes) at 6 and 12 months compared to baseline.
- Changes in gastric motility, volume, accommodation, and constructed gastroplasty on MRI at 6 months compared to baseline.
- Changes in gastric emptying evaluated by gastric emptying study at 6 months compared to baseline.
- Changes in liver biochemical panel, and glucose homeostasis parameters at 6 months compared to baseline between the two groups.

Safety

- The incidence, frequency, and severity of adverse events related to treatment with the device will be reported throughout the duration of the study.
- Goal is <5% rate of serious adverse events related to the device or procedure (as determined by the site PI). Serious adverse events will be classified in the Adverse Events table.

Study Setting

The study will be conducted at 1 US center, Mayo Clinic in Rochester, MN. The maximum enrollment will be limited to 24 participants. The expected enrollment period is 6 months.

Subjects

Participants will be adult patients (Ages 21 ≥ and ≤ 65) with a BMI ≥ 30 and ≤ 40 kg/m^2 that meet the eligibility criteria below. All eligibility criteria must be met at the time of randomization.

Inclusion Criteria

1. Age 21-65
2. BMI ≥ 30 and ≤40 kg/m²
3. Willingness to comply with the substantial lifelong dietary restrictions required by the procedure.
4. History of failure with non-surgical weight-loss methods.
5. Willingness to follow protocol requirements, including signed informed consent, routine follow-up schedule, completing laboratory tests, and completing diet counseling.

6. Residing within a reasonable distance from the investigator's office and able to travel to the investigator to complete all routine follow-up visits.
7. Ability to give informed consent.
8. Women of childbearing potential (i.e., not post-menopausal or surgically sterilized) must agree to use adequate birth control methods.

Exclusion Criteria

1. History of foregut or gastrointestinal (GI) surgery (except uncomplicated cholecystectomy or appendectomy).
2. Prior gastrointestinal surgery with sequelae, i.e. obstruction, and/or adhesive peritonitis or known abdominal adhesions.
3. Prior open or laparoscopic bariatric surgery.
4. Prior surgery of any kind on the esophagus, stomach, or any type of hiatal hernia surgery.
5. Any inflammatory disease of the gastrointestinal tract including severe (LA Grade C or D) esophagitis, Barrett's esophagus, gastric ulceration, duodenal ulceration, cancer, or specific inflammatory disease such as Crohn's disease or celiac disease.
6. Potential upper gastrointestinal bleeding conditions such as esophageal or gastric varices, congenital or acquired intestinal telangiectasis, or other congenital anomalies of the gastrointestinal tract such as atresias or stenoses.
7. Gastrointestinal stromal tumors, history of premalignant gastric lesions (intestinal metaplasia), history of familial and nan-familial adenomatous syndromes.
8. A gastric mass or gastric polyps > 1 cm in size.
9. A hiatal hernia > 4cm of axial displacement of the z-line above the diaphragm or severe or intractable gastro-esophageal reflux symptoms.
10. A structural abnormality in the esophagus or pharynx such as a stricture or diverticulum that could impede passage of the endoscope.
11. Achalasia or any other severe esophageal motility disorder
12. Severe coagulopathy.
13. Insulin-dependent diabetes (either Type 1 or Type 2) or a significant likelihood of requiring insulin treatment in the following 12 months or a HgbA1C≥9.
14. Subjects with any serious health condition unrelated to their weight that would increase the risk of endoscopy.
15. Chronic abdominal pain.
16. Motility disorders of the GI tract such as gross esophageal motility disorders, gastroparesis or intractable constipation.

17. Hepatic insufficiency or cirrhosis.
18. Use of an intragastric device prior to this study due to the increased thickness of the stomach wall preventing effective suturing.
19. Active psychological issues preventing participation in a life-style modification program as determined by a psychologist.
20. Patients unwilling to participate in an established medically supervised diet and behavior modification program, with routine medical follow-up.
21. Patients receiving daily prescribed treatment with high dose aspirin (> 81mg daily), anti-inflammatory agents, anticoagulants, or other gastric irritants.
22. Patients who are unable or unwilling to take prescribed proton pump inhibitor medication.
23. Patients who are pregnant or breast-feeding.
24. Patients currently taking weight-loss medications or other therapies for weight loss within the prior 6 months.
25. Subjects with severe cardiopulmonary disease or other serious organic disease which might include known history of coronary artery disease, myocardial infarction within the past 6 months, poorly controlled hypertension, required use of NSAIDs.
26. Subjects taking medications on specified hourly intervals that may be affected by changes to gastric emptying, such as anti-seizure or anti-arrhythmic medications.
27. Subjects who are taking corticosteroids, immunosuppressants, and narcotics.
28. Symptomatic congestive heart failure, cardiac arrhythmia, or unstable coronary artery disease.
29. Pre-existing respiratory disease such as moderate or severe chronic obstructive pulmonary disease (COPD) requiring steroids, pneumonia, or cancer.
30. Diagnosis of autoimmune connective tissue disorder (e.g. Systemic lupus erythematosus, scleroderma) or immunocompromised.
31. Specific diagnosed genetic disorder such as Prader Willi syndrome.
32. Eating disorders including night eating syndrome (NES), bulimia, binge eating disorder, or compulsive overeating.
33. Known history of endocrine disorders affecting weight such as uncontrolled hypothyroidism.
34. At the discretion of the PI for subject safety
35. If minority inclusion population target of 10% has not been reached by the 90% enrollment mark (example 21 of 24 subjects), the remaining enrollments will be reserved for minority subjects (example 3 of 24 subjects).

TRIAL PROCEDURES

Informed Consent

Prior to being enrolled in the trial, study participants must consent to participate after the nature, scope, and possible risks of the trial have been explained and outlined in an understandable form to them per the requirements of the IRB. Participants are free to withdraw consent at any time.

After reading the Informed Consent Form (ICF) document, the participant must sign and date the latest approved version of the ICF before any study procedures are performed (electronic via compliant system such as Docusign, or wet-signed copy prepared in Participant Tracking System (Ptrax). A copy of the signed consent document will be accessible for the participant, and the original signed consent form will be retained by the study team.

Where possible, “remote” visits such as via phone or video call will be acceptable across the schedule of events to streamline coordination efforts and adapt to any unexpected conditions such as isolation protocol.

Study Timeline

The study timeline is depicted in Figure 1.

Figure 1. Study Flow Diagram

Screening and Eligibility assessment

Screening will be conducted by the investigator or the co-investigator and documented on the Investigator delegated/medically qualified team member intake form (conventionally known as PI Intake Form) and Screening Labs form. Screening must occur no more than 45 days prior to randomization.

Screening will include the following:

1. Sign informed consent form
2. Screening exam and intake by the investigator or co-investigator
3. Height, weight, and BMI; waist and hip circumference; vital signs (blood pressure and pulse)
4. Dietary screening intake and approval
5. Laboratory tests (after 8 hours fasting)
    - **CBC**: hemoglobin, hematocrit, white blood cell count, mean corpuscular volume, platelets
    - **Chemistry panel**: sodium, potassium, chloride, CO2, BUN, creatinine, fasting glucose, fasting insulin, SGOT/AST, SGPT/ALT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, fasting lipids profile (total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol), Ferritin, B12, C-reactive protein.
    - **Coag**: INR, PTT
    - **Urinalysis**
    - **HgbA1C**
    - **H. Pylori Breath Test**. **Patients with a positive h-pylori breath test will be treated and eradication must be confirmed with a stool antigen after treatment and prior to randomization**
    - **EKG** for all patients
    - **Urine pregnancy test** for women of child-bearing potential[a]
    - **MRI** at baseline to evaluate gastric anatomy, gastric motility, and gastric accommodation.
    - **Gastric emptying scintigraphy** at baseline to evaluate gastric emptying. Gastric emptying scintigraphy will be conducted according to current Mayo Clinic Rochester clinical protocol.
6. Questionnaires
7. Psychological evaluation and approval: Study psychologists will use their standard clinical evaluations for bariatric interventions.

Within one week (7 calendar days) of completion of the screening tests, the PI will review the results and determine the participant's eligibility. The center will inform the participant of their screening results within 10 days of completing testing. Any abnormal lab results will be communicated to the participant by delegated personnel, and they will be required to notify their primary care provider (PCP) for any further action that may be necessary. All potential participants who qualify for randomization based on the initial

[a] Childbearing potential to be defined as women who are not yet post-menopausal who are not consistently utilizing an acceptable form of contraception. Acceptable forms of contraception to include hormonal methods such as oral contraceptives, patches, injections, vaginal ring, or implants, hormonal or copper intrauterine device, or history of surgical sterilization including tubal ligation or hysterectomy.

screening assessments will have the chance to review any questions with the study staff, as well as a recap of the follow-up schedule, and they will then receive their randomization assignment.

Recruitment efforts will be made by working with Mayo Clinic's Research Recruitment Services to develop marketing materials including a recruitment flyer in both print and digital formats, a social media recruitment plan leveraging Mayo Clinic's enterprise social media accounts for recruitment and other potential tactics to be determined after recruitment begins, directed towards the goal of boosting minority inclusion to be at least representative of the local population. Data will be pulled during the time of IRB submission and included to establish general targets justifying Exclusion #35 to help reserve spots for enrollment that are in-line with a representative population if they are not met by a certain threshold. At the time of this writing, Rochester, MN has demonstrated approximately 10% minority population.

Randomization

Participants will be randomly assigned to treatment or control group with a 1:1 allocation per a computer-generated randomization using variable block randomization.

Participants will be blinded to the results of randomization. They will remain blinded until the end of the study, or if there is medical or surgical safety concern. If any SAEs occur, subjects may be unblinded as defined by the Clavien-Dindo Grade III or above. Unblinding of subjects will be reported to IRB per local site IRB guidelines, if not meeting the criteria above. Measures will be taken to minimize or avoid bias in the study using "masking/blinding procedures." Randomization assignment will be recorded in the EDC and subject tracking, but will not be recorded within the EMR to reduce clinical team exposure to their randomized status for follow-up care. Research teams will not be blinded to the randomization results. Subjects will be asked to confirm with their study team if they have become aware of the procedure.

Participants will proceed to a brief visit with the dietician to review the post-op liquid diet, and the procedure (ESG or HAPC/ESG) will be scheduled within 60 days of randomization.

Trial Intervention

Participants will report to the procedure suite within 60 days of randomization. Participants of child-bearing potential will be required to have a pregnancy test within 7 days of the scheduled ESG or combined HAPC and ESG. Participants taking medications for hypertension and/or type II diabetes will be instructed to notify their prescribing physician of their procedure and to discuss any necessary medication changes for the post-op period.

The ESG or combined HAPC and ESG will be conducted in Saint Marys Hospital at the Mayo Clinic in Rochester, Minnesota. Within two hours prior to the procedure, IV access will be obtained, IV hydration initiated, and a transdermal scopolamine patch placed for patients 65 years of age or younger (this will be removed in 24 to 48 hours after the procedure). Scopolamine can precipitate delirium in elderly patients, and hence we will avoid using them in patients older than 65 years of age. After Hybrid ESG or traditional ESG patient will be monitored for 24-48 hours to ensure patient is able to tolerate liquid diet and discharge timing is to be determined on individual basis per the site primary investigator.

Prior to ESG or combined HAPC and ESG, a standard upper endoscopy is performed to rule out any contraindications. All procedures will be done under general anesthesia with endotracheal intubation and utilizing CO2 insufflation. During the procedure, IV hydration will be continued, and patients will be given the following: one dose of IV antibiotics (Zosyn, Ceftriaxone, or Ciprofloxacin), 8 mg of IV Zofran, and 8 mg of Decadron. A minimum of two liters of IV hydration (either normal saline or lactate ringers) should be administered in the perioperative recovery period before discharge. Sequential compression devices

(SCDs) will be used perioperatively to decrease the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Patients will be prescribed the following medications or equivalent after the procedure to manage expected post-procedural symptoms:

- Zofran 4mg rapid dissolving pills taken every 6 hours as needed for nausea for 7 days
- Phenergan 25mg suppositories taken twice daily as needed for nausea for 7 days
- Low dose liquid narcotic taken every 6 hours as needed for pain for 5 days
- Omeprazole 40mg capsule to be opened and mixed with smooth, semi-liquid food for the first 7 days after ESG or combined HAPC and ESG, then taken as whole capsule daily for 12 months from date of ESG or combined HAPC and ESG.
- Ativan 0.5 mg taken orally once daily for up to 3 days as needed for intractable nausea or anxiety.

Admission for a 23-hour observation for symptom management is optional but permissible. All patients will be given instructions prior to being discharged from the facility to help manage post-procedural symptoms, including nausea, vomiting and/or abdominal pain. Study staff will call patients once between 18-36 hours after the procedure to assess symptoms and to relay any issues to the PI. If the PI feels it is necessary to see a patient in clinic, an unscheduled visit will be scheduled appropriately.

All patients will go on a 6-week transitional diet consisting of 4 weeks of full liquid protein shakes and 2 weeks of soft pureed diet. The transitional diet is designed to allow suture healing and incorporation within the plicated gastric wall. After the transitional diet period, all patients will be on a low-calorie healthy diet personalized by the dietician according to individual patients' needs conducive to weight loss. Physical activity, including 150 minutes of aerobic exercise per week, will be encouraged and assessed for compliance during the study. It may be recommended for patients to take two chewable multivitamins and one calcium plus vitamin D supplement daily starting within 1 week of the ESG or combined HAPC and ESG.

All patients will undergo a standard moderate intensity life-style intervention administered over 12 visits in the first year after procedure. Participants will be required to follow up with their prescribing physician to make any necessary changes to their hypertension and/or type II diabetes medications at 3, 6, 9 and 12 months. Completion of patient follow-up with providers for medication adjustment will be captured with completion of the appropriate CRF at the corresponding visits. In the event that participants are unable to contact their physician or participants are experiencing symptoms related to the medication dosing requiring urgent action, the study team will make any necessary changes in their medication dosing and document these changes appropriately in the relevant CRFs. Any medication changes will be monitored and recorded by the study team. Laboratory testing will be obtained as detailed in the study schedule of events

Participants will return for follow-up visits per the schedule of events below. For all visits with the exception of weeks 1 and 4, an in-window visit will be considered as reporting for follow-up visits within a two-week window of the visit date.

At the time of the 6-month visit, each subject's 6-month de-identified EGD video will be shared with an external center for an additional blinded assessment of the primary endpoint (suture durability) by a qualified endoscopist. Each video will be classified objectively according to the aspect of the gastric tissue and the sutures (intact, partially intact, or open). This sharing will take place through Mayo SimpleShare system.

Schedule of Events (SOE)

Study Activity	**Screening & Enroll.**	**Rand.**	**Procedure**	**Post-Op Call**	**Week 1**	**Week 4**	**Week 8**	**Week 12**	**Weeks 16, 20**	**Week 26 (Month 6)**	**Weeks 30, 36, 42, 48**	**Week 52 (Year 1)**	**Unscheduled Visit**
Visit Number	-2	-1	0	1	2	3	4	5	6,7	8	9,10,11,12	13	
In-Window Day Range	**45 to Rand.**	**60 to Proc.**	**0◊**		**+/- 2**	**+/- 3**	**+/- 14**						
Informed Consent Form (ICF)	X												
Complete Physical Exam (CPE)*	X											X	X
Focused Physical Exam *					X								
EKG	X												
Formal nutritional assessment	X												
Formal psychology evaluation	X												
Pregnancy test **	X												
Laboratory tests [+] H-Pylori breath test (baseline only)	X									X		X	
Questionnaires [++]	X							X		X		X	
Inclusion/Exclusion	X												
Procedure Assessment Form			X										
GERD Questionnaire & Activity Assessment Form	X				X	X	X	X	X	X	X	X	X
Weight, Height (Screening only), BMI, Waist and Hip Circumference Form	X		X		X	X	X	X	X	X	X	X	X
Vital Signs Form	X		X		X	X	X	X	X	X	X	X	X
Adverse Events Form			X	X	X	X	X	X	X	X	X	X	X
Medication Form	X		X	X	X	X	X	X	X	X	X	X	X
Randomization (ESG vs Hybrid ESG/APC) †		X											
EGD			X							X			
MRI	X									X			
Gastric emptying scintigraphy***	X									X			
Post-enrollment Nutrition/Exertion/Satiety counseling and assessment † †		X			X	X	X	X	X	X	X	X	
Subject Satisfaction Questionnaire												X	
Inter-observation of EGD										X			

* Performed by Investigator or delegated medically qualified team member
** Females of childbearing potential only
***POC Urine Pregnancy Test required 48 hours prior to procedure (if not within window from blood test)
+ CBC, electrolytes, BUN, creatinine, HbA1c, fasting blood sugar, fasting insulin, fasting lipids profile (total cholesterol, LDL, HDL, triglycerides), INR, PTT, ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, CRP, B12, ferritin
++Eating and weight patterns questionnaire + hospital anxiety and depression questionnaires (only at baseline), Impact of Weight on Quality of Life-Lite (IWQOL-Lite), Short Form (36) Health Survey (SF36), Patient Health Questionnaire 9 (PHQ9), Pittsburg Sleep Quality Index (PSQI), Three Factor Eating Questionnaire (TFEQ)
† To occur after all screening assessments are complete; within 45 days of screening evaluations

† † To discuss upcoming post-op diet and exertion

◊ If the procedure is unable to be performed within the 105 day in-window range due to factors outside the control of the study team (patient testing positive for COVID-19, delays associated with H. pylori eradication testing, or limitations of the procedural schedule), the PI will assess if any baseline laboratory tests must be repeated prior to the procedure for subject safety.

Participant Retention

All patients will be encouraged to complete study follow-up, and all reasonable efforts will be made to ensure completeness of follow-up.

It is understood that study participants may withdraw consent for study participation at any time irrespective of their reasons. The investigators may also withdraw a participant from the study in order to protect their safety, and/or if they are unwilling or unable to comply with the required study procedures.

In the event of a patient withdrawing from the trial, the reason for withdrawal must be documented on the CRF.

Replacement of withdrawn subjects

Patients withdrawn prior to undergoing combined HAPC and ESG or ESG alone will count towards the target accrual. Screen failed patients will not count towards target accrual. New patients will be randomized to target accrual of 24 total patients receiving combined HAPC and ESG or ESG alone. The power and sample size calculation includes sufficient patients to yield power assuming some post-intervention dropout.

Source Documentation

Study source worksheets and/or electronic documentation in the medical record will be used as source documentation for the trial for all participant follow-up visits. Source documentation from the electronic medical record will be required for the procedure(s), medications, and any serious adverse medical events. REDCap will be used for collection of electronic sources and verified by PI attestation as the eCRF. If unavailable to conduct electronic source, physical CRF source worksheets will be available and can be added to the eCRF for investigator attestation.

PROTOCOLS FOR PROCEDURE AND IMAGING

HybridAPC (HAPC) Application

HAPC will be performed in conjunction with ESG in patients in the treatment group. The location is from the level of the incisura all the way to the fundus. The pattern includes 3 rectangular APC ablation zones created on the anterior, greater curvature and posterior surface of the stomach. The HAPC is composed of a submucosal lift followed by ablation. The default setting of the APC is 50 Watts, 1 L/min flow, but it may be adjusted within normal clinical limits dependent on participant anatomy and tissue response. After ablation, ESG will be performed in standard fashion.

Measurement of Gastric Accommodation by Dynamic MRI

Gastric MRI will only be performed in patients who can safely undergo MRI. It will be performed at both baseline and 6 months for subjects randomized to either study arm. Subjects will be kept NPO after midnight and scanned with MRI using a torso phased array coil. If the 3T magnet (Phillips) is not available, a 1.5T magnet will be used. Before, and after a meal (296 ml Ensure mixed with 4ml gadolinium, i.e., 300 ml), static and dynamic imaging sequences will be acquired using available MR sequences to assess respectively gastric volumes and motility. No intravenous contrast will be administered. Postprandial accommodation will be calculated as the difference between postprandial and fasting volumes (Neurogastroenterol Motil 2009; 21:42–51; American Journal of Physiology. 2014;307:G582-G587). Likewise, gastric motility (i.e., contractile frequency, amplitude and velocity) will be analyzed with established approaches (Neurogastroenterol Motil 2011;23(7):617-e252).

Gastric Emptying Scintigraphy

Gastric emptying scintigraphy will be performed at baseline and at 6 months for subjects randomized to either study arm. Imaging will begin immediately after consumption of a standardized meal including 1 mCi Tc-99m labeled sulfur colloid in two eggs accompanied by one slice of white bread and a glass of skim milk. For patients unable to consume any individual component of the meal substitutions will be made according to clinical protocol. Dual isotope acquisition of anterior and posterior views of the abdomen will be acquired, with view times to be within +/- 15 minutes of the hour. Images will be acquired Baseline (0), 1, 2, 3 and 4 hours following ingestion of the radiolabeled meal. Results will be interpreted according to institutionally established normal ranges. Geometric means of decay-corrected counts in anterior and posterior gastric regions of interest will be used to estimate the proportion of 99mTc emptied at each time point.

Screening & Enrollment

This will include a patient visit for procedures mentioned in section 5.3. This includes:

- Signing informed consent form
- Screening exam and intake by the investigator or co-investigator
- Baseline anthropomorphic and vital signs data
- Baseline laboratory testing, including pregnancy test if female of childbearing potential
- Baseline EKG
- Baseline MRI
- Baseline gastric emptying scintigraphy
- Baseline questionnaires.
- Baseline nutritional assessment
- Baseline psychological evaluation and approval

Randomization

After randomization, patients will have a brief post-enrollment nutrition/exertion/satiety counseling and assessment.

Procedure

This includes a patient visit for procedure which may or may not include an admission for a 23-hour observation for symptom management, further elaborated in section 5.5.
Anthropomorphic and vital signs data will also be collected on procedure day.

Post-Op Call

This is a telephone visit which will include review of adverse events and medications.

Week 1

This will include:

- Focused physical examination
- Anthropomorphic and vital signs data
- Review of adverse events and medications
- Nutritional counseling and assessment.

Week 4(Month 1)

This will include:

- Anthropomorphic and vital signs data
- Review of adverse events and medications
- Nutritional counseling and assessment.

Week 8(Month 2)

This will include:

- Anthropomorphic and vital signs data
- Review of adverse events and medications
- Nutritional counseling and assessment.

Week 12 (Month 3)

This will include:

-
- Questionnaires
- Anthropomorphic and vital signs data
- Review of adverse events and medications
- Nutritional counseling and assessment.

Weeks 16, 20

These will include:

- Anthropomorphic and vital signs data
- Review of adverse events and medications
- Nutritional counseling and assessment.

Week 26 (Month 6)

This will be a comprehensive visit, including:

- Complete physical examination
- Anthropomorphic and vital signs data
- Review of adverse events and medications
- Laboratory testing
- Questionnaires
- EGD, to be performed clinically
- MRI
- Gastric emptying scintigraphy
- Nutritional counseling and assessment.
- Inter-observation of deidentified EGD video by qualified endoscopist

Weeks 30, 36, 42, 48

These will include:

- Anthropomorphic and vital signs data
- Review of adverse events and medications
- Nutritional counseling and assessment.

Week 52 (Year 1)

This will include:

- Complete physical examination
- Anthropomorphic and vital signs data
- Review of adverse events and medications
- Laboratory testing
- Questionnaires
- Nutritional counseling and assessment.

Unscheduled Visit

Any unscheduled visits will include a complete physical examination collection of anthropomorphic and vital signs data and review of adverse events and medications.

DATA MONITORING AND SAFETY REPORTING

Data and Safety Monitoring

This study will adhere to an IRB approved data safety monitoring plan (DSMP) to ensure sufficient oversight of the following areas of study conduct: subject safety, data integrity, subject privacy, data confidentiality, product accountability, study documentation and study coordination. Monthly meetings will be held with the Principal Investigator in attendance to review study conduct, with additional meetings to occur as needed to address time sensitive matters including adverse events or any deviations. Internal monitoring will be conducted following the accrual of the first subject, with additional monitoring to be undertaken on a quarterly basis thereafter. All adverse events, deviations and unanticipated problems affecting subject safety will be reported according to the requirements of the IRB of record. Ongoing assessment of AEs by the PI will determine if any of the stopping rules have been triggered.

7.11 Stopping rules

The study will be stopped if a) one death attributed to the procedure or the device, b) >2 of Grade IV AEs has occurred, and c) > 4 Grade III or more AEs occur.

Adverse Events

7.2.1 Definitions

The following definitions will be used:

7.2.1.1 Adverse Events:

Only untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) related to the study intervention. Each subject will be followed closely to ensure safety.

Adverse events will be classified using the Clavien-Dindo classification in Figure 2.

Figure 2. Adverse Event (AE) Clavien-Dindo Classification Grading

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

7.2.1.2. Serious Adverse Event (SAE):

An adverse event that meets one of the following criteria

- Led to death
- Resulted in serious deterioration in the health of the subject that results in:
    - Life-threatening illness or injury
    - Permanent impairment of a body structure or a body function
    - The need for in-patient care or prolongation of hospitalization (this does not include the optional 23 hours observation admission after ESG or re-tightening procedure).
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- **Planned hospitalization for a pre-existing condition, or a procedure required by the trial protocol, without serious deterioration in health, is not considered a serious adverse event**

Unanticipated problems, SAEs and AEs will be reported to governing IRBs per local guidelines.

For the purpose of the study, an adverse event is considered severe if it is grade ≥ 3 on the Clavien-Dindo classification.

7.2.1.3 Device-Related Adverse Event (DRAE):

An adverse event related to the use of the medical device. This definition includes any events resulting from incorrect delivery and operation of the device and/or of its approved accessories, or any malfunction of the device or its components. This definition also includes any event resulting from user error or from intentional misuse of the device.

7.2.1.4 Serious Device-Related Adverse Event (SDRAE):

Any untoward medical occurrence that can be attributed wholly or partly to the device, which resulted in any of the characteristics of a serious adverse event as described above.

7.2.1.5 Unanticipated Adverse Device Effects (UADE):

Any adverse device effect which by its nature, incidence, severity, or outcome, has not been identified under the SAE section 6.2.

Protocol Deviation

All protocol deviations will be documented with the subject number and date of the protocol deviation. The following information will be documented for each protocol deviation:

- Inclusion/Exclusion exceptions or violations, including subject did not sign informed consent prior to study admission
- Follow-up visit not performed or Follow-up outside of window
- Required testing or questionnaire not performed
- Other (Describe)

Protocol deviations will be reported to the IRB at the time of continuing review unless they are determined to rise to the level of a major deviation and/or impact subject safety. In the event of a major deviation a report is to be made to the IRB within 5 working days. All deviations are to be recorded in the EDC.

Risk/Benefit evaluation

ESG is an established procedure that has an excellent safety profile and has been shown to demonstrate significant weight loss. APC is approved for use in the GI tract and has also been shown to have a good safety profile. Combining ESG with HAPC technique could enhance the durability of this procedure by enabling approximation of submucosal surfaces for enhanced gastroplasty healing. This could help maximize the metabolic benefits of gastric mucosal revitalization in conjunction with the restrictive effects of ESG for enhanced weight loss, durability, and metabolic benefits of the combined procedure while minimizing the risk of weight recurrence previously reported with the traditional ESG. Since both procedures have an established good safety profile, hence minimizing the risks about using them in conjunction.

STATISTICAL ANALYSIS

Power and Sample Size
The primary endpoint for power and sample size is durability of plications on repeat endoscopy 6 months after initial procedure with HAPC and ESG and ESG alone. Another primary endpoint for power and sample size is %TBWL at 6 and 12 months.

We plan a 1:1 randomization scheme that allocates to either HAPC ESG (12 patients) or ESG alone (12 patients). Given the pilot nature of this trial, no formal power calculation is feasible or warranted.

Statistical Analysis
Statistical analyses of randomized groups at 6 and 12 months will be performed based on a modified intent-to-treat (mITT) principle for efficacy analyses. Patients randomized but subsequently withdrawn or identified as meeting exclusion criteria prior to intervention (as applied to both the treatment and control arms) will be excluded from the analysis if the reason for exclusion is documented and unrelated to the randomized arm.

8.2.1 Primary Aim

The primary outcomes are durability of plications and endoscopic sutures on repeat endoscopy at 6 months, in the two randomized arms.

8.2.2 Secondary Aims

Continuous secondary outcomes, including %TBWL[b], %EWL[c], change in systolic and diastolic blood pressure and change in HbA1c, QOL questionnaires such as the SF-36, IWQOL, PHQ-9, and eating behavior scores will be compared between treatment arms using ANCOVA with adjustment for the same variables specified in the primary analysis.

Binary outcomes, including proportion with ≥25% reduction in %EWL and incidence of esophagitis will be compared between treatment arms by Pearson Chi-square test.

Among all subjects, %EWL will be compared at 6 and 12 months between both arms of the study.

8.2.3 Secondary Analyses
A per-protocol analysis will compare randomized groups among protocol adherent patients – here, defined among as those actually receiving the procedure and making ≥ 80% follow-up visit in both groups. Modified ITT will be considered the primary approach for all efficacy analyses and will include patients who actually received the intervention regardless of adherence to follow-up visits. Safety endpoints and adverse events may be evaluated based on treated group (per-protocol).

Additional outcomes and analyses not specified here are considered exploratory and post-hoc and will be clearly identified as such in any publications.

---

[b] %TBWL defined as [(pre-operative weight - post-operative weight)/(pre-operative weight)] x 100
[c] % EWL defined as [(pre-op weight – follow up weight)/(pre-op weight – ideal body weight)] X 100
Note: "Ideal body weight" of BMI 25

Missing Data
The primary analysis uses a hierarchical regression model, assuming post-randomization dropout is missing at random (MAR) among subjects completing at least 1 of the planned follow up visits.
Patients excluded after randomization and before intervention on the basis of identified exclusion criteria will be excluded from analyses; reasons for meeting exclusion criteria will be documented. Patients that withdraw/dropout between randomization and intervention are assumed to be missing completely at random. However, a sensitivity analysis will compare withdrawn subjects to participating subjects and perform analyses under MAR (including multiple imputation) assumptions if these subjects appear different or if dropout occurs at substantially different rate in one arm compared to the other. Participating patients who dropout prior to the first follow up visit will be analyzed similarly.

Randomization and Data Collection
Stratified block randomization schedules will be uploaded to REDCap. Data will be collected in REDCap data collection forms.

Interim Analysis
No interim analysis will be performed for efficacy endpoints. Adverse events will be monitored throughout and discussed with the data monitoring committee.

ETHICAL CONSIDERATIONS

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

STUDY FINANCES

Funding Source

The study is financed through the funding partner, Erbe Elektromedizin GmbH, and the Mayo Clinic Rochester.

Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

Subject Stipends or Payments

Subjects will not receive remuneration for taking part in this study.

The procedure costs and all other costs associated with imaging, testing, procedure day, and follow-up visits will be covered by the funding partner, Erbe Elektromedizin GmbH, and Mayo clinic Rochester. Subjects will not pay for any procedure or test performed as part of the study and outlined in the protocol.

REFERENCES

1. Hales CM, Carroll MD, Fryar CD, et al. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018. NCHS Data Brief 2020:1-8.
2. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. N Engl J Med 2019;381:2440-2450.
3. Flegal KM, Kit BK, Orpana H, et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309:71-82.
4. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. The New England journal of medicine 2006;355:763-78.
5. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373:1083-96.
6. Wadden TA, Butryn ML, Wilson C. Lifestyle Modification for the Management of Obesity. Gastroenterology 2007;132:2226-2238.
7. Kheniser K, Saxon DR, Kashyap SR. Long-Term Weight Loss Strategies for Obesity. The Journal of Clinical Endocrinology & Metabolism 2021;106:1854-1866.
8. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. New England Journal of Medicine 2021;384:989-1002.
9. Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA 2021;325:1403-1413.
10. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397:971-984.
11. Enebo LB, Berthelsen KK, Kankam M, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: a randomised, controlled, phase 1b trial. Lancet 2021;397:1736-1748.
12. Bal BS, Finelli FC, Shope TR, et al. Nutritional deficiencies after bariatric surgery. Nature Reviews Endocrinology 2012;8:544-556.
13. Proietto J. Why is treating obesity so difficult? Justification for the role of bariatric surgery. Medical Journal of Australia 2011;195:144-146.
14. Hedjoudje A, Abu Dayyeh BK, Cheskin LJ, et al. Efficacy and Safety of Endoscopic Sleeve Gastroplasty: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol 2020;18:1043-1053.e4.
15. Itani MI, Farha J, Sartoretto A, et al. Endoscopic sleeve gastroplasty with argon plasma coagulation: a novel technique. Journal of Digestive Diseases 2020;21:664-667.
16. Mahmoud T, Vargas EJ, Ghazi R, et al. The Osculating Circles Gastroplasty: A Novel Endoscopic Submucosal Resection Enhanced Endoluminal Suturing for Obesity. Gastroenterology 2021;161:1806-1808. e1.
17. Jirapinyo P, de Moura DTH, Dong WY, et al. Dose response for argon plasma coagulation in the treatment of weight regain after Roux-en-Y gastric bypass. Gastrointestinal Endoscopy 2020;91:1078-1084.
18. Itani MI, Farha J, Sartoretto A, et al. Endoscopic sleeve gastroplasty with argon plasma coagulation: A novel technique. J Dig Dis 2020;21:664-667.
19. Lee JH, Johannes RS, Van Dam J, et al. 7087 Argon plasma coagulation in endoscopic therapy. Gastrointestinal Endoscopy 2000;51:AB264.
20. Mitchell NS, Catenacci VA, Wyatt HR, et al. Obesity: overview of an epidemic. The Psychiatric clinics of North America 2011;34:717-732.

21. Tremmel M, Gerdtham U-G, Nilsson PM, et al. Economic Burden of Obesity: A Systematic Literature Review. International Journal of Environmental Research and Public Health 2017;14:435.
22. Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. Annals of Internal Medicine 2001;134:1-11.
23. Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489-96.
24. Pi-Sunyer X, Blackburn G, Brancati FL, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes care 2007;30:1374-83.
25. Dalle Grave R, Calugi S, Centis E, et al. Lifestyle modification in the management of the metabolic syndrome: achievements and challenges. Diabetes, metabolic syndrome and obesity : targets and therapy 2010;3:373-385.
26. Kheniser K, Saxon DR, Kashyap SR. Long-Term Weight Loss Strategies for Obesity. J Clin Endocrinol Metab 2021;106:1854-1866.
27. Kheniser K, Saxon DR, Kashyap SR. Long-Term Weight Loss Strategies for Obesity. The Journal of clinical endocrinology and metabolism 2021;106:1854-1866.
28. Bult MJ, van Dalen T, Muller AF. Surgical treatment of obesity. Eur J Endocrinol 2008;158:135-45.
29. Chang S-H, Stoll CRT, Song J, et al. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA surgery 2014;149:275-287.
30. Lupoli R, Lembo E, Saldalamacchia G, et al. Bariatric surgery and long-term nutritional issues. World journal of diabetes 2017;8:464-474.
31. English WJ, DeMaria EJ, Brethauer SA, et al. American Society for Metabolic and Bariatric Surgery estimation of metabolic and bariatric procedures performed in the United States in 2016. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery 2018;14:259-263.
32. Wadden TA, Tronieri JS, Butryn ML. Lifestyle modification approaches for the treatment of obesity in adults. The American psychologist 2020;75:235-251.
33. Brunaldi VO, Neto MG. Endoscopic Procedures for Weight Loss. Current Obesity Reports 2021;10:290-300.
34. Courcoulas A, Abu Dayyeh BK, Eaton L, et al. Intragastric balloon as an adjunct to lifestyle intervention: a randomized controlled trial. Int J Obes (Lond) 2017;41:427-433.
35. Aljiffry M, Habib R, Kotbi E, et al. Acute Pancreatitis: A Complication of Intragastric Balloon. Surg Laparosc Endosc Percutan Tech 2017;27:456-459.
36. Rahman AA, Loi K. Gastric Perforation as a complication of intragastric balloon. Surg Obes Relat Dis 2018;14:719-722.
37. Gleysteen JJ. A history of intragastric balloons. Surg Obes Relat Dis 2016;12:430-5.
38. Abu Dayyeh BK, Rajan E, Gostout CJ. Endoscopic sleeve gastroplasty: a potential endoscopic alternative to surgical sleeve gastrectomy for treatment of obesity. Gastrointestinal Endoscopy 2013;78:530-5.
39. Sharaiha RZ, Kedia P, Kumta N, et al. Initial experience with endoscopic sleeve gastroplasty: technical success and reproducibility in the bariatric population. Endoscopy 2015;47:164-6.
40. Abu Dayyeh BK, Acosta Cardenas AJ, Camilleri M, et al. Endoscopic Sleeve Gastroplasty Alters Gastric Physiology and Induces Loss of Body Weight in Obese Individuals. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2015.
41. Sharaiha R. Managing Obesity With Endoscopic Sleeve Gastroplasty. Gastroenterology & hepatology 2017;13:547-549.

42. Jirapinyo P, de Moura DTH, Thompson CC. Endoscopic submucosal dissection with suturing for the treatment of weight regain after gastric bypass: outcomes and comparison with traditional transoral outlet reduction (with video). Gastrointestinal endoscopy 2020;91:1282-1288.
43. Zenker M. Argon plasma coagulation. GMS Krankenhaushygiene interdisziplinar 2008;3:Doc15-Doc15.
44. Marchesini SD, Baretta GAP, Cambi MPC, et al. Endoscopic plasma argon coagulation in treatment of weight regain after bariatric surgery: what does the patient think about this? Arquivos brasileiros de cirurgia digestiva : ABCD = Brazilian archives of digestive surgery 2014;27 Suppl 1:47-50.
45. Dhindsa BS, Saghir SM, Naga Y, et al. Efficacy of transoral outlet reduction in Roux-en-Y gastric bypass patients to promote weight loss: a systematic review and meta-analysis. Endoscopy international open 2020;8:E1332-E1340.
46. Storm AC, Thompson CC. Endoscopic Treatments Following Bariatric Surgery. Gastrointest Endosc Clin N Am 2017;27:233-244.
47. Jaruvongvanich V, Vantanasiri K, Laoveeravat P, et al. Endoscopic full-thickness suturing plus argon plasma mucosal coagulation versus argon plasma mucosal coagulation alone for weight regain after gastric bypass: a systematic review and meta-analysis. Gastrointest Endosc 2020;92:1164-1175.e6.
48. Catalano MF, Rudic G, Anderson AJ, et al. Weight gain after bariatric surgery as a result of a large gastric stoma: endotherapy with sodium morrhuate may prevent the need for surgical revision. Gastrointestinal Endoscopy 2007;66:240-245.
49. Baretta GAP, Alhinho HCAW, Matias JEF, et al. Argon Plasma Coagulation of Gastrojejunal Anastomosis for Weight Regain After Gastric Bypass. Obesity Surgery 2015;25:72-79.