Bariatric Embolization of ArTeries with imaging visibLe EmbolicS

(BEATLES)

Protocol Number: BAE2

National Clinical Trial (NCT) Identified Number: 04197336

Principal Investigator: Clifford Weiss, MD

IDE Sponsor: Clifford Weiss, MD

Funded by:

Biocompatibles UK Ltd (internal study number BTG-001933-01)

and Siemens Healthcare

Version Number: v4

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Table of Contents	Taste Test has been removed	
1.3	SOA: • Taste test (deleted) • Gastric Meds (added) • Pain Prophylaxis (added)	
2.3	Pain Management: IV acetaminophen (added)	
4.1	Overall Design: 5 run-in participants (removed) 10 pilot patients (added)	
5.2	Exclusion Criteria Addition: Use of anti-obesity medications in the 12 months prior to screening	

5.5	**Payment table revised: removal of the taste test**	
6.3	**Measures to Minimize Bias: Site Training Randomization and Blinding:** **5 run-in patients (removed)** **10 pilot patients (added)**	
8.2.12	**Removal Taste Test Description**	
8.2.19	**Removal of Taste Test associated questionnaires**	
9.3	**Populations for Analyses:** **5 run-in (removed)** **Ten pilot (added)**	
9.4.6	**Planned Interim Analyses:** **5 run in patients (removed)** **Ten (10) pilot patients (added)**	
10.1.6	**Safety Oversight:** **first 5 (non-randomized) (removed)** **first 10 (non-randomized) pilot participants (added)**	

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator, who in this case is also the Investigational Device Exemption (IDE) sponsor, will assure that no deviation from, or changes to the protocol will take place without prior agreement from or notification of the funding agency and documented approval from the FDA and Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

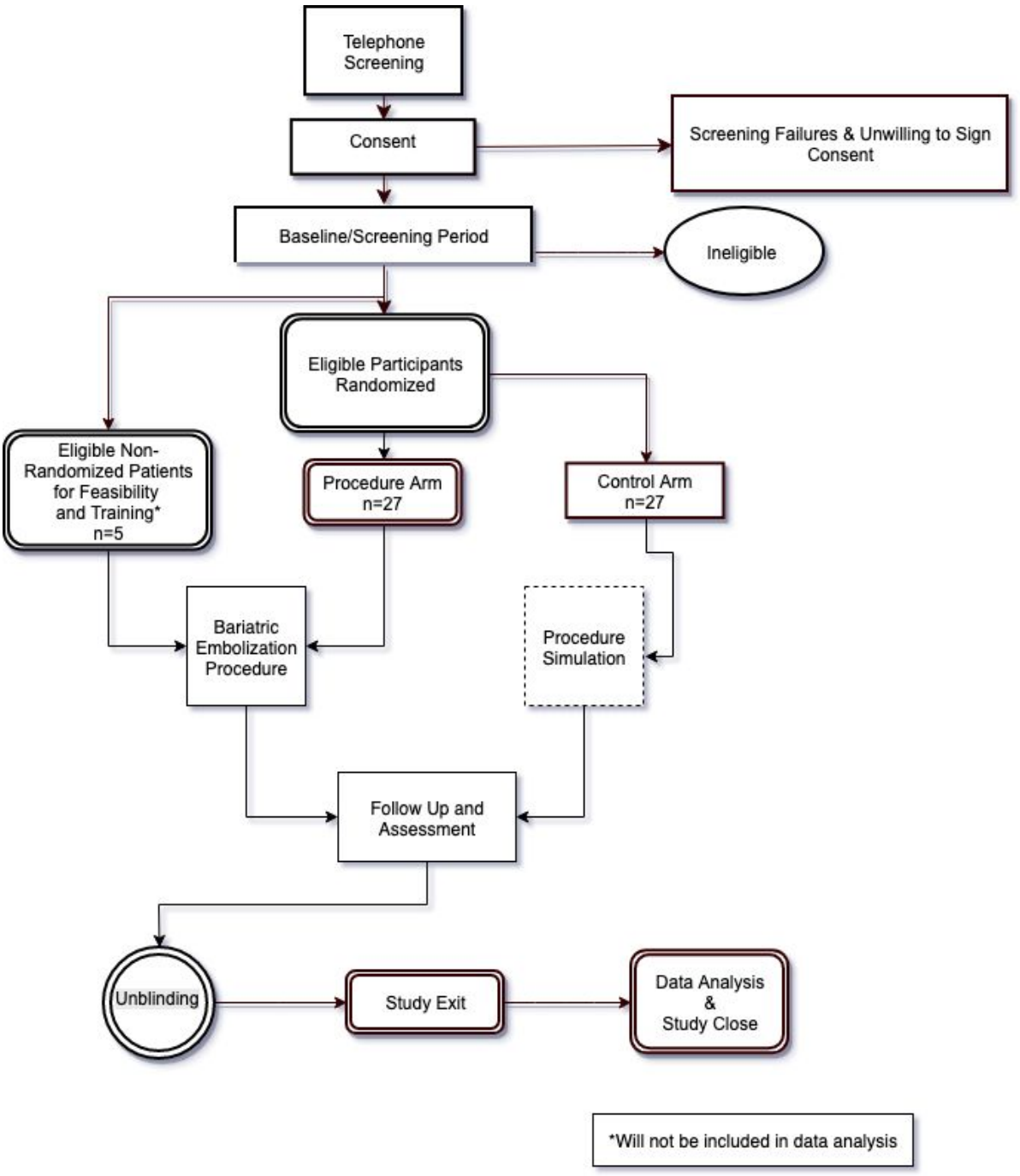
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Bariatric Embolization of ArTeries with imaging visibLe EmbolicS (BEATLES)
Study Description:	The BEATLES study is an investigator-initiated, prospective, double-blinded, randomized, sham-controlled study that will assess the impact of bariatric embolization on the systemic levels of obesity-related hormones and, as a consequence, on weight loss. The goal of this study is to help treat obesity combining a lifestyle program and a minimally invasive, angiographic (i.e., through blood vessels) approach.
Objectives:	Primary Objective: To determine the efficacy of the BAE procedure using radiopaque 100-200 µm microspheres (BTG-001933) for weight loss in obese patients. Secondary Objectives: To determine the safety and further explore the efficacy of the BAE procedure using radiopaque 100-200 µm microspheres (BTG-001933) for weight loss in obese patients
Endpoints:	Primary Endpoint: Change in body weight 12 months after randomization Primary Safety Endpoints: All adverse events until the end of the study (12 months)

	Secondary Endpoints: 1) All adverse events until day 30 post embolization 2) Change in body weight at timepoints other than 12 months 3) Percentage change in body weight 4) Achievement of >5% reduction in body weight 5) Percentage excess weight loss (EWL) 6) Change in multi-compartment body fat composition as measured by MRI
Study Population:	59 adult men and women, ages 21-70 years, with a body mass index (BMI) ≥35 kg/m^2 and otherwise suitable for protocol therapy at the Johns Hopkins Hospital
Phase:	2
Description of Sites/Facilities Enrolling Participants:	1 site: Johns Hopkins Hospital
Description of Study Intervention:	Minimally invasive, non-surgical, angiographic bariatric embolization (BAE) of the left gastric and/or gastroepiploic arteries using investigational 100-200 μm radiopaque microspheres (BTG-001933, Biocompatibles UK, Ltd)
Study Duration:	3 years
Participant Duration:	12 months

1.2 SCHEMA


Telephone Screening
Consent
Screening Failures & Unwilling to Sign Consent
Baseline/Screening Period
Ineligible
Eligible Participants Randomized
Eligible Non-Randomized Patients for Feasibility and Training* n=5
Procedure Arm n=27
Control Arm n=27
Bariatric Embolization Procedure
Procedure Simulation
Follow Up and Assessment
Unblinding
Study Exit
Data Analysis & Study Close
*Will not be included in data analysis

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Pre-Procedure	Procedure Day	Follow-Up					
			1 week (±1 day)	2 weeks (±3 days)	4 weeks (±3 days)	3 months (±14 days)	6 months (±14 days)	12 months (±14 days)
Informed Consent	X							
Demographics	X							
History & Physical	X	X	X	X	X			
Study Team Visit[β]	X		X	X	X	X	X	X
Psychological Evaluation[Δ]	X				X	X	X	X
Blood & Urine Tests	X	X***	X	X	X	X	X	X
Pregnancy Test*	X	X***				X	X*	X*
Stool Occult Blood Study	X							
3D CTA	X							
Gastric Emptying*	X					X	X	
Endoscopy with biopsy	X					X[◊]	X*	X*
Quality of Life Questionnaires	X		X	X	X	X	X	X
Hormone Tests	X		X	X	X	X	X	X
MRI	X					X	X	X
Weight Management Counseling (Johns Hopkins Healthful Eating, Activity & Weight Program) †	8 visits over 2 months[α]		Months 1-2: MD/WC alternating weekly, starting w/ WC; Months 3-5: MD 2x/mo; Month 6: MD 1x/mo, WC 1x/mo; Month 7-12: MD 1x/mo					
Randomization		X						
Gastric Meds	X	X	6 weeks post procedure					
Bariatric Embolization**/ Sham Procedure		X						
CT/CBCT		X						
Pain Prophylaxis		X	AM post BAE only					
Assessment of AEs		X	X	X	X	X	X	X
Lose It! Food Log	Start 7 days prior to first WM visit		Subject completes food log on Lose It! application daily, reviewed at each provider WM visit					
ASA 24	X			X	X	X	X	X
Hunger Satiety Scale	X				X	X	X	X
HealthReel	X					X	X	X
Unblinding Survey					X			X

*If applicable, e.g. in diabetic patients only (gastric emptying), female of child-bearing ability (pregnancy tests at baseline and 3 months), in case of symptoms (endoscopy in months 6 and 12), in case of endoscopy (pregnancy tests in months 6 and 12)
**Participants will be admitted to the hospital after the embolization or sham procedure.
***These labs will be performed if previous test results are >30 days old.
†Weight management schedule: weekly visits with the Johns Hopkins Healthful Eating, Activity & Weight Program during 8-week run-in and first 8 weeks post-procedure, consisting of either a visit with a physician or a weight check with a nurse. (MD: physician visit, WC: weight check)
αWeekly visits with the Johns Hopkins Healthful Eating, Activity & Weight Program ,with the following schedule: week 1: intake with provider (1 hour); weeks 2-3: weight check (15 minutes); week 4: provider follow-up visit (15 minutes); weeks 5-6: weight check (15 minutes); weeks 7-8: provider follow-up visit (15 minutes)

βStudy team visits will consist of a meeting with one of the interventional radiology fellows or study physicians as well as the study coordinators in order to check in with the patient regarding how they are doing. The post-procedural study team visits at 2- and 4-weeks post-procedure will include a physical exam.
∆Psychology visits may be completed remotely (i.e. telehealth) if clinically indicated—this will be at the discretion of the study psychologists.Follow-up visits may be conducted more frequently than specified (i.e. optional 9-month visit).

2 INTRODUCTION

2.1 STUDY RATIONALE

The BEATLES study is an investigator-initiated, prospective, double-blinded, randomized, sham-controlled study that will assess the impact of bariatric embolization of the left gastric artery and/or gastroepiploic arteries on the systemic hormonal levels of obesity and weight loss. The goal of this study is to help treat obesity using a minimally invasive, non-surgical, angiographic (i.e., through blood vessels) approach. This Investigational Device Exemption (IDE) is requested to support the use of 100 – 200µm BTG-001933 microspheres in bariatric artery embolization for the treatment of obesity. The BTG-001933 microsphere (Biocompatibles UK, LTD) is an investigational device based on the legally marketed LC Bead LUMI™ (K152157, K162373), which has an approved indication for use of embolization of hypervascular tumors and arteriovenous malformations. The BTG-001933 microsphere is the result of modification of the LC Bead LUMI™ with respect to bead size range and iodine content. These device modifications may facilitate and optimize imaging techniques associated with the planned procedure.

2.2 BACKGROUND

2.2.1 STOMACH IS AN ENDOCRINE ORGAN

Although there are >40 hormones that limit food intake, there is only one hormone, ghrelin, that has been shown to be orexigenic, i.e., stimulate food intake. Discovered by Kojma et al. in the rat stomach, it has been shown to induce growth hormone release by acting on the growth hormone secretagogue receptor (GHS-R) in the hypothalamus or anterior pituitary.(1) Since the identification of this neuropeptide, extensive data in both animals and humans have shown its potent orexigenic effects.(2) Mechanisms to antagonize or suppress the effects of ghrelin on the central nervous system have resulted in dramatic weight loss and change in appetite in various studies.(2,3) In studies performed in human volunteers, intravenous ghrelin stimulates meal initiation, with nearly half of volunteers describing a sensation of hunger and a compensatory increase of 28% in caloric intake.(4) Further evaluation has shown that in humans, there is a consistent pattern of ghrelin levels rising shortly before, and falling immediately after, every meal. In situations such as weight loss, there is a compensatory increase in ghrelin levels, which may contribute to the difficulty in maintaining the lower body weight.(5) In many but not all obese participants, food fails to suppress systemic ghrelin levels, which can impair postprandial satiety and initiate overeating.(6) Due to the potent orexigenic effect of ghrelin, this hormone is a target for the treatment of obesity and weight loss. However, although various reports of ghrelin suppression have been described, none are clinically practical.

2.2.2 ANATOMY OF THE GASTRIC FUNDUS

The stomach is classically separated into seven major sections: cardia, fundus, antrum, pylorus, lesser curvature, greater curvature, and angularis (Figure 1A). While each section of the

stomach has a unique role in the digestive process, the fundus serves as the epicenter for the neuroregulatory pathway involved in satiety and appetite stimulation.(7-10) Ghrelin is expressed mainly in the fundus, which contains 10 to 20 times more ghrelin per gram of tissue than the duodenum, the next richest source, and has a higher level of growth hormone secretagogue (GHS) receptor activation than the hypothalamus.(11, 12) Notably, the vascular supply to the gastric fundus is distinct, identifiable, and can be accessed with a catheter using a percutaneous approach. The dominant flow to the fundus arises from the left gastric artery, which is the first branch off the celiac axis (Figure 1B).

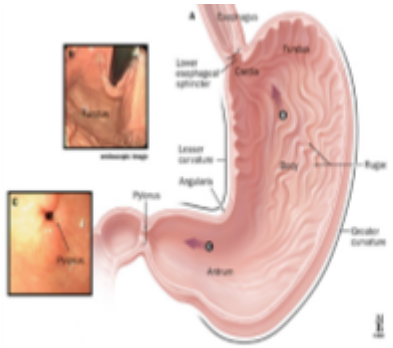


Figure 1A: Anatomic drawing of the different sections of the stomach.

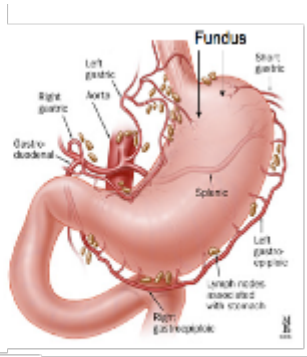


Figure 1B: Vascular supply to the stomach.

Transcatheter gastric arterial embolization has been performed for at least three decades, and has been shown to be effective at controlling acute gastrointestinal hemorrhage. Embolization works by effectively interrupting blood flow. In addition, the gastrointestinal (GI) tract has a rich, collateral blood supply, with extensive vascular arcades that allow for safe embolization without ischemia. Thus, bariatric arterial embolization (BAE) is already a clinically viable procedure, and is currently the standard of care in participants whose condition is refractory to endoscopic control of gastrointestinal bleeding.

2.2.3 GHRELIN SUPPRESSED AFTER GASTRIC BYPASS SURGERY

More recently, ghrelin has been found to have a significant role in the long-term effect of weight loss following bariatric surgery. Since bariatric surgery isolates the gastric fundus from ingested nutrients, ghrelin profiles are shown to be lower by 77% compared to those in controls.(7,13-15) Furthermore, the normal diurnal pattern of ghrelin is interrupted, and the meal-initiated fluctuations are blunted.(7,13) Based on these findings, achieving low systemic ghrelin levels should be considered as a strategy to control obesity and maintain weight loss.

2.2.4 OVERVIEW OF BEATLES

Obesity is defined as a body mass index (BMI) ≥30 kg/m^2 and with a subclass of obesity known as morbid or severe obesity (BMI of ≥40 kg/m^2). These are major issues in medicine for both participants and medical providers with >36% of the US population affected. Obesity is one of the biggest causes of preventable chronic diseases and healthcare costs in the USA. Obese adults spend 42% more on direct healthcare costs and morbidly obese adults overall have 81% higher healthcare costs than non-obese adults. Obesity is currently treated with dietary, pharmacological, and/or surgical approaches that are often unsuccessful or are associated with additional risks. As the incidence and prevalence of obesity and obesity-related diseases are steadily increasing, there is a growing need to detect the key risk factors involved in disease development and modify standard treatment procedures and protocols.

The most successful long-term strategy continues to be bariatric and metabolic surgeries, such as sleeve gastrectomy and Roux-en-Y gastric bypass (RYGBP). The NIH recommends bariatric

surgery for participants with a BMI of 40 kg/m^2 or greater or a BMI of 35 kg/m^2 or greater and obesity related comorbidities. These surgeries enable participants to lose between 50% and 75% of excess body weight. Despite this success, participants are apprehensive and do not undergo bariatric surgery with the biggest fear being the many complications that come with the procedure. Studies have shown that 57-77% of participants are not interested in bariatric surgery although they qualify.(16)

With the concern of complications from bariatric surgery, interest in endoscopic bariatric techniques has increased over the years. They have been shown to be efficacious, reversible, relatively safe, and cost effective. Further, these techniques offer a therapeutic window for some participants who may otherwise be unable to undergo bariatric surgery. The American Society for Gastrointestinal Endoscopy have approved endoscopic procedures, such as balloon therapy, for participants with BMI in the 30-40 kg/m^2 range.(17,18) However, the products used in these therapies also have several limitations primarily the inability to provide long term weight loss given the temporary nature of these balloons.(19) Common adverse events following intragastric balloon insertion include abdominal pain (33.7%), gastroesophageal reflux disease (18.3%), anorexia, and nausea (29%). Severe complications such as gastric ulcers (2%), small bowel obstruction (0.3%), perforation (0.1%), balloon migration (1.4%), and death (0.08%) are less common. Early balloon removal occurred in 9.1% of the study participants due to participant intolerance.(20)

In a pilot study to assess safety and efficacy (BEAT Obesity), 20 morbidly obese participants with a BMI of ≥40 kg/m^2 with no other comorbid conditions underwent bariatric embolization and were followed for 12 months. Participants were embolized with 300-500 µm Embospheres. None of the 20 participants in the BEAT Obesity trial (the largest prospective trial to date) had any major adverse events. Any gastric ulcers that occurred (40%) were asymptomatic and were completely healed by three months after the procedure.(21)

There were many limitations of this study including the absence of a control cohort and non-compliance amongst study participants. A target population of participants with a BMI of 40 kg/m^2 and above was too high considering the bariatric embolization procedure is comparable to endoscopic bariatric therapies rather than bariatric surgery. BEAT Obesity excluded participants with comorbidities, such as those who suffer from diabetes, who may greatly benefit from this procedure and are often the target population for endoscopic/surgical bariatric therapies. A larger bead size of 300-500 µm was specifically chosen compared to preclinical data and prior clinical reports due to concerns of gastric ischemia and ulceration. However, smaller bead size produces greater weight loss and hormonal shifts.(22)

We hypothesize that transvascular bariatric embolization results in safe and effective weight loss in obese participants compared to control subjects.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The prior BEAT Obesity clinical trial allowed for identification of three major areas of risk for bariatric embolization: Gastric Ulcers, Increased Radiation Dose in Obese Participants, and Non Target Vascular Embolization (NTE).

Gastric Ulcers

As was done in the BEAT Obesity Trial, all participants will be treated with gastroprotective agents to mitigate the risks for gastric ulcers. In addition, all participants will be heavily screened to identify and exclude all participants who would be at higher risk for gastric ulcerations.

Currently, arterial embolization with 100-300 μm particles is routinely clinically performed for a number of indications (including embolization of the gastric fundus for control of hemorrhage), and has not been shown to have significant clinical sequelae of tissue necrosis or infarction. In fact, all the investigators in the BEATLES trial have embolized the gastric fundus for gastrointestinal hemorrhages with particles, and have not seen any cases of gastric ulceration/perforation. In the prior BEAT Obesity trial, the procedure was carried out safely with a 300-500 μm embolic, and 8/20 participants had superficial gastric mucosal ulceration seen at 2 weeks, all of which were healed at 3 months. In all reported studies world-wide published at this time, transient superficial mucosal ulcers were commonly observed and none were deemed major complications or major adverse events.

Radiation Dose

The mean radiation dose in the prior BEAT Obesity trial was 5042.6 (±996) mGy, well below NRC reporting thresholds. There were no radiation associated injuries in any participants observed at follow-up clinic visits. The BEATLES study will use an in-procedure CT scan to serve the same purpose as did the cone beam computed tomography (CBCT) did in the BEAT Obesity Trial, to minimize the risk of NTE and to determine fundal perfusion. The modified fluoroscopic time and software algorithms to reduce radiation exposure developed in the BEAT Obesity Trial will be used in the BEATLES study.

Non Target Vascular Embolization (NTE)

Due to the proximity of the dorsal pancreatic artery to the left gastric artery, and the pancreatico-duodenal arcade to the gastroepiploic artery, it is possible that the risk of pancreatitis is still relevant. In the BEAT Obesity trial, one participant had post-procedural elevation in pancreatic enzymes, which might have been attributable to reflux/NTE during distal gastroepiploic arterial embolization. To minimize such reflux and NTE, the spheres are now routinely diluted in a larger volume of contrast/saline to prevent proximal clumping, which can cause reflux. Also, 3D CTA prior to the procedure and CBCT were used in all five participants to further map the vascular anatomy. However, due to technical/anatomical challenges, an anti-reflux system was used in one vessel. Moving forward, the use of preventative measures may still be employed to mitigate NTE. Of course, the use of an imaging-visible embolic will be essential to determine the location of embolic delivery, and to fully assess any NTE.

There are certain risks and discomforts that may be associated with this research study. Previous studies have shown the following side effects:

- Some participants had mild abdominal discomfort after the procedure, lasting less than two weeks.
- In initial clinical experiments, around 40% of participants had mild gastric irritation with minor ulceration assessed by endoscopy, which had healed by the time of the repeat examination at three months.

- 20% of participants reported mild to moderate constipation for up to three months after the procedure.
- In addition, mild delays in gastric emptying occurred in 1/20 participants with resolution at six months. This might result in nausea, vomiting, and/or abdominal pain.
- Side effects may result from particles lodging into areas outside the targeted stomach area (NTE), resulting in blockage of the blood vessels to the bowel, liver, gallbladder, pancreas, spleen, groin, bladder, pelvis, or legs. If severe, they may need to be corrected by surgery.
- Other possible events include nausea, vomiting, inflammation of the stomach, ulceration, bleeding from the stomach, stomach rupture or death. Bleeding from the area in the thigh or wrist where the catheter is inserted, allergic reaction to the contrast agent, an effect on fertility, damage (perforation) to a blood vessel that can lead to hemorrhage, a temporary contraction in a blood vessel (vasospasm), or bruise in the groin or wrist area (hematoma) are also possible.
- Blood clots in the veins (deep vein thrombosis) or lungs (pulmonary embolism) or death are unlikely.

It is possible that there will be other short-term or long-term complications, including the inability to have future gastric surgery. Patients will be educated that, at a minimum, a gastric angiogram is recommended prior to any future gastric surgery.

Risks from Gastro-protective Medications

Omeprazole is a proton pump inhibitor that works by decreasing the amount of acid produced by the stomach and is typically used to treat certain conditions including, but not limited to, gastric and duodenal ulcers, erosive esophagitis, and gastroesophageal reflux disease (GERD). Sometimes, omeprazole is used in combination with antibiotics (e.g., amoxicillin, clarithromycin) to treat ulcers associated with infection caused by the H. pylori bacteria. Omeprazole is also used to treat dyspepsia, a condition that causes sour stomach, belching, heart burn, or indigestion.

The most frequent significant adverse effects occurring in at least 1% of participants in the BEAT Obesity Trial taking omeprazole included:

- Central nervous system: headache (7%), dizziness (2%)
- Respiratory: upper respiratory infection (2%), cough (1%)
- Gastrointestinal: abdominal pain (5%), diarrhea (4%), nausea (4%), vomiting (3%), flatulence (3%), acid regurgitation (2%), constipation (2%)
- Neuromuscular & skeletal: back pain (1%), weakness (1%)
- Dermatologic: rash (2%)

There are other very rare, potential concerns of taking omeprazole related to adverse effects:

- Bacteria-associated diarrhea
- Increased risk of pneumonia
- Osteoporosis-related fractures
- Hypomagnesemia
- There is concern regarding vitamin B12 and iron malabsorption, but the effects seem to be clinically insignificant, especially when supplemental therapy is provided.

Sucralfate is used to treat and prevent duodenal ulcers, as well as other conditions as determined by a doctor. Sucralfate works by forming a “barrier” or “coating” over the ulcer, protecting the ulcer from stomach acid and allowing it to heal. Sucralfate contains an aluminum salt. The most common side effects seen are constipation (2-3%) and bezoar formation. Less commonly reported effects include flatulence, headache, hypophosphatemia, and dry mouth.

Omeprazole and sucralfate will be prescribed to every participant. Antibiotics will only be prescribed to treat an accompanying infection.

Pain Management
IV acetaminophen (or a similar pain management medication) will given prophylactically for pain during and after the procedure. Dosage of IV acetaminophen will follow standard of care guidelines for use and will be paid for by the study. The most common adverse event associated with IV acetaminophen are nausea, vomiting, headache, and insomnia.

CT Angiography

Allergy to the contrast agent or injury from radiation exposure during imaging are possible. If a participant has an allergic reaction to the contrast agent, he/she will not be allowed to continue with the embolization procedure.

Radiation Exposure

This research study includes exposure to radiation from x-rays or gamma-rays (CT scan, gastric-emptying study, bariatric embolization). This radiation exposure is for research purposes only, and is not part of the participants’ medical care. X-rays and gamma rays can damage the genetic material (DNA) in cells. At low doses, cells usually can repair this damage.

The radiation exposure that participants will receive is an average of 4.2 rem, depending on the participants’ diabetic status, weight, and procedural difficulty. This exposure is more than the 0.3 rem that the average person in the US gets each year from natural sources like the sun, outer space, air, food, and soil. Most participants will receive less than the 5 rem of radiation that is allowed each year for people who are exposed to radiation in their jobs.

The radiation exposure described here is what participants will get from this research study only. It does not include any exposure the participants may have received or will receive from other tests outside of this study that are a part of their medical care. Radiation risk builds up with each exposure. Participants should think about their own history of radiation exposure from tests (like x-rays or CT scans) when deciding about the radiation in this study.

Endoscopy with biopsy

Upper endoscopy is a very safe procedure. However, it carries a very small risk of complications. Rare complications include:

- **Bleeding.** Risk of bleeding complications after endoscopy is increased because the procedure involves removing a piece of tissue for testing (biopsy) or treating a digestive system problem. In rare cases, such bleeding may require a blood transfusion.

- **Infection.** Most endoscopies consist of an examination and biopsy, and risk of infection is low. The risk of infection increases when additional procedures are performed as part of the endoscopy. Most infections are minor and can be treated with antibiotics. Primary physicians may give participants preventive antibiotics before their procedure if they are at higher risk of infection.
- **Tearing of the GI tract.** A tear in the esophagus or another part of the upper digestive tract may require hospitalization, and sometimes surgery to repair it. The risk of this complication is very low — it occurs in an estimated three to five of every 10,000 diagnostic upper endoscopies.

Other Risks

Participants may also experience some brief and/or minor discomfort associated with the tests required.

- Taking blood may cause discomfort, bleeding, or bruising where the needle enters the body. In rare cases, it may result in fainting. There is a small risk of infection.
- While every reasonable effort will be made to ensure confidentiality of protected and sensitive personal medical information, there is a risk that this confidentiality is compromised, although the study doctors to not expect this to occur.
- Participants may get tired or bored when asked questions or when completing questionnaires. Participants do not have to answer any question they do not want to answer.
- Future possibility of weight loss surgery may be limited after participating in this investigational study, as the degree of risk of complications are not known and will need to be discussed with the surgeon.
- Risks of MRI may include patients being bothered by the noise and experiencing claustrophobia.
- There may be side effects and discomforts that are not yet known.

2.3.2 KNOWN POTENTIAL BENEFITS

There is no guarantee of specific benefit to the participants enrolled in this study, however all participants will receive free weight management care from the Johns Hopkins Hospital comprehensive weight management center and free psychological counseling through the study. Data collected in this clinical investigation will provide a foundation for future efficacy studies and analyses.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The trial is being done to determine the efficacy and safety of the BAE procedure using the modified microsphere. All identified risks will be mitigated as described above. Active surveillance by the DSMB of known risks as outlined and with respect to complications listed in the IFU will occur with mitigation or stopping plans in place should any of the known risks exceed expected thresholds. It is concluded that the value of the information to be gained outweighs the risks of participation in the study based on the prior experience of the investigators and the anticipated low frequency of expected events.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the efficacy of the BAE procedure using radiopaque 100-200 µm microspheres (BTG-001933) for weight loss in obese patients Primary Safety: To determine the safety of the BAE procedure using radiopaque 100-200 µm microspheres (BTG-001933) for weight loss in obese patients	Change in body weight 12 months after randomization Frequency of AEs 12 months after randomization	This is the standard for weight management trials. Safety determination is required for investigation of this non-FDA approved device.
Secondary		
To determine the safety and further explore efficacy of the BAE procedure using radiopaque 100-200 µm microspheres (BTG-001933) for weight loss in obese patients	1) All adverse events (AEs) until 30 days post embolization 2) Change in body weight at timepoints other than 12 months 3) Percentage change in body weight 4) Achievement of >5% reduction in body weight 5) Changes in multi-compartment body fat composition as measured by MRI	1: Safety determination is required for investigation of this non-FDA approved device. 2: Weight measurements are standard for weight management trials. 3 & 4: These endpoints are often used in phase 3 weight management trials and will allow for comparison to FDA-approved obesity treatments. *5:* MRI is a new measure of BMI and will be done specifically to measure and compare detailed compartmental weight changes between the intervention and control groups. This endpoint will also provide insight into patient selection for future trials.
Tertiary/Exploratory		
To explain and support findings of the primary analyses and for suggesting further hypotheses for later research.	1) Change in blood pressure 2) Lipid/lipoprotein profile 3) Change in obesity-related hormones a. Ghrelin, LEAP2, leptin, glucagon-like peptide-1 (GLP-1), peptide YY (PYY) etc. 4) Improvement in markers of obesity-related complications (glycaemia as assessed by HbA1c, fasting glucose and insulin, change in medication effect score (MES)) 5) Food intake 6) Hunger/satiety assessments 7) Quality of life parameters survey: IWQOL-Lite 8) Results from endoscopy	1-4, 9: Laboratory and blood pressure data will permit measures of cardiovascular and metabolic health. In addition, the obesity-related hormones believed to be the underlying mechanism of BAE success, will be monitored over time to test this hypothesis. 5-7: Quality of life and hunger/satiety/food intake measurements are standard assessments in weight loss trials. 8: Endoscopy results will be evaluated as a measure of safety to determine degree of ulceration and other potential gastric pathology.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	9) Ghrelin expression in pre- and post-embolization fundal biopsy samples 10) Changes in taste perception 11) Analysis of image post procedure using CT: bead distribution, fundal coverage 12) Embolization endpoint (occlusion, recanalization)	10: Evidence in prior work indicates taste changes after bariatric surgery. 11-12: Stasis and dosing in interventional radiology will be measured and compared to more traditional techniques to determine if image-visible embolics are more precise and safe and if degree of fundal coverage correlates with the procedure outcome.

4 STUDY DESIGN

4.1 OVERALL DESIGN

We hypothesize that transvascular bariatric embolization of the left gastric and/or gastroepiploic arteries will results in safe and effective weight loss in obese participants compared to control subjects.

The BEATLES study is an investigator-initiated, prospective, phase 2, single-site, double-blinded, randomized, sham-controlled study that will assess the impact of bariatric embolization on the systemic hormonal levels of obesity and weight loss in 54 obese participants (BMI ≥35 kg/m^2) at post-procedure weeks 1 and 2, and months 1, 3, 6, and 12. There will be 10 pilot patients (See Statistical Analysis below for sample size calculations) for a total of 59 participants. Participants will be followed with study outcomes assessed for a period of 12 months. The duration of the study will be approximately three years.

The goal of this study is to help treat obesity using a minimally invasive, angiographic (i.e., through blood vessels) approach. This study will be conducted under an FDA Investigational Device Exemption (IDE) to support the use of 100 – 200 µm BTG-001933 microspheres in bariatric artery embolization for the treatment of obesity. The BTG-001933 microsphere (Biocompatibles UK, LTD) is an investigational device based on the legally marketed LC Bead LUMI™ (K152157, K162373), which has an approved indication for use of embolization of hypervascular tumors and arteriovenous malformations. The BTG-001933 microsphere is the result of modification of the LC Bead LUMI™ with respect to bead size range and iodine content. These device modifications may facilitate and optimize imaging techniques associated with the planned procedure.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Due to the psychological basis for weight loss, a sham control procedure is required for comparison. All patients will receive weight management support, which is routine care for this patient population.

4.3 JUSTIFICATION FOR DOSE

The standard embolization technique utilized for the study was chosen based on animal studies to create ischemia. Ischemia is a reduction in blood flow, which is the mechanism that causes the cells in target area (fundal region of stomach) to down regulate ghrelin hormone production without necrosis. During the embolization process beads will be infused (under CT imaging) until stasis of anterograde arterial flow is achieved. It is believed that lower ghrelin levels result or correlate with suppressed appetite or lowered hunger response.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male or female, aged ≥21 and ≤70 years
2. Willing, able, and mentally competent to provide written informed consent
3. Obese patients with a BMI ≥35 kg/m^2
4. Weight ≤400 lb
5. Vascular anatomy (including celiac, hepatic, and gastric arteries) that in the opinion of the interventional radiologist is amenable to bariatric embolization, as assessed via 3D CT angiography
6. Suitable for protocol therapy, as determined by the interventional radiology investigator
7. Adequate hematologic (neutrophils>1.5x10^9/L, platelets>70x10^9/L, INR<1.5), hepatic (bilirubin≤2.0mg/dL, albumin≥2.5g/L), and renal (estimated GFR>60mL/min. 1.73m^2) function
8. For females of reproductive potential: agreement to use of highly effective contraception for duration of study participation
9. Patients who have failed conservative weight loss therapies such as supervised low-calorie diets combined with behavior therapy and exercise
10. Live or work within 65 miles of the enrolling institution in case a catastrophic post-embolization event occurs

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

Exclusion Criteria (Medical):

1) Hb A1c greater than 8%

2) Patients who are currently taking either Insulin or Sulfonylureas (medication changes are allowed)
3) Prior history of gastric, pancreatic, hepatic, and/or splenic surgery
4) Prior radiation therapy to the upper abdomen
5) Prior embolization to the stomach, spleen, or liver
6) Cirrhosis
7) Known portal venous hypertension
8) Active peptic ulcer disease
9) Significant risk factors for peptic ulcer disease, including daily NSAID use
10) Large hiatal hernia, defined as >5 cm in size
11) Active H. pylori infection
12) Known aortic pathology, such as aneurysm or dissection
13) Renal insufficiency, as evidenced by an estimated glomerular filtration rate of <60 mL/min
14) Major comorbidity, such as active cancer, significant cardiovascular disease, or peripheral arterial disease
15) Pregnancy
16) Pre-existing chronic abdominal pain
17) Positive stool occult blood study
18) GI bleeding or bleeding diathesis within 5 years
19) Weight loss (intentional or unintentional) of more than or equal to 5% of body weight in the 6 months prior to randomization
20) A weight loss greater than 6lb during the weight management run-in
21) Use of anti-obesity medications in the 12 months prior to screening.
22)
23) Endoscopic findings that would preclude BAE (at the discretion of the study team)
24) History of gastric motility disorders or an abnormal nuclear gastric motility examination (to be performed in diabetic subjects only)
25) ASA Class 4 or 5 (very high risk surgical candidates: class 4=incapacitating disease that is a constant threat to life) at the time of screening for enrollment into the study – this exclusion criterion exists, because of the possibility that surgical intervention will be needed if the study intervention subsequently leads to severe adverse effects
26) Inflammatory bowel disease
27) Autoimmune disease or HIV+
28) History of allergy to iodinated contrast media
29) Failure to comply with pre-procedure weight management “run-in”, or other pre-procedural visits (specifically, participants must complete 80% of weight management and Lose It! Food tracking, and 100% of one-time visits, i.e. MRI, CTA, endoscopy)
30) Applicability of any contraindication regarding patient’s vasculature as per Instruction for Use
31) Inability to have an MRI scan (i.e., metal implants or claustrophobia)
32) Smokers/vapers/tobacco use
33) Active or new-onset endocrine disorders other than diabetes (stable disease acceptable)
34) Other unforeseen conditions that may make patients unsuitable for the procedure (study team discretion)

Exclusion Criteria (Psychiatric):

35) As determined by clinical judgment based on Clinical Interview, psychological/behavioral measures, medical records, previous mental health records/other collateral information (as available) and consistent with DSM -5 criteria:

36) Diagnosis of severe mental illness (i.e., chronic psychotic spectrum disorders, clinically significant mood disorders) AND/OR one or more of the following:
    - Evidence of active relapse or active impairing symptoms (e.g., suicidal ideation, audio or visual hallucinations, paranoia, thought disturbance, severe impairment)
    - Evidence of minimal supports or limited adherence to ongoing mental health care
    - Failure to provide comprehensive aftercare plan that includes emergency plan for addressing future mental health relapse
    - History of treatment refractory mental illness/recurrent relapse (multiple suicide attempts or inpatient psychiatric hospitalizations in the past 5 years)
    - Within past 3 years: Inpatient psychiatric hospitalization
    - Within past 5 years: Suicide attempt
    - Declining to provide mental health records, a letter of support from mental health professionals, or consent for verbal consultation with mental health professionals when determined to be essential to evaluation.
    - Cognitive impairment, if judged to have
    - Limited capacity to make informed decision about procedure and inability to verbalize an understanding of the surgical procedure, risks and benefits.
    - Inability to demonstrate an understanding of the permanency of lifestyle change required
    - History of Anorexia or History of/Active Bulimia: If determined to be of low enough severity not to be a clear contraindication, minimum of 5 years abstinence from bulimia; current moderate to severe binge eating or night eating syndrome
    - Active or History of Substance Abuse with less than 5 years of abstinence
    - Current use of tricyclic anti-depressants or steroids, psychiatric medications associated with weight gain

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Undergo medical therapy consisting of lifestyle counseling and weight management.
- Diabetic subjects will have their medications managed by their diabetes specialist, per routine care, as defined by American Diabetes Association guidelines.
- Eat nothing after midnight prior to their clinic visits.
- Agree to use birth control for the duration of the study (women of fertile age).
- Avoid use of tobacco products for the duration of the study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of medications or other modifiable conditions (including but not limited to weight changes, non-cancerous failed endoscopy, active H. Pylori infection, uncontrolled glucose) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The targeted patient cohort is men and women aged between 21 and 70 years of various racial and ethnic backgrounds. Vulnerable patients (pregnant women, those who lack consent capacity, prisoners, children, employees, etc.) will be excluded as per the inclusion and exclusion criteria.

It is anticipated that approximately 1300 patients will be pre-screened to enroll 59 eligible subjects (based on prior experience in the BEAT Obesity trial) over a 24-month period. All subjects will be enrolled at the Johns Hopkins Hospital. Pre-screening will utilize an existing registry of patients from previous trials and patient referrals (weight management clinic referrals and self-referrals from advertising campaign). Identified or referred patients will be screened by phone using a telephone script.

Subjects will be followed for a period of 12 months. Retention strategies will include collecting multiple methods for contacting each participant and visit reminders. Subjects will receive payments of up to $945 after the bariatric embolization (or control) procedure per the 12-month period, using the payment scheme tabulated below. Payment is given at 5 different intervals. Each test or log must be completed within the allotted range in order to receive payment. Payment may be prorated for weight management visits. For example, if a participant attended 4 weight management visits instead of 5 during weeks 4-8, they may receive $40 during that time.

Weeks 1-3	**Weeks 4-8**	**Months 3-5**	**Months 6-11**	**Month 12**
Food Log $30	Food Log $20	Food Log $20	Food Log $30	Food Log $40
Hunger Satiety $30	Hunger Satiety $20	Hunger Satiety $20	Hunger Satiety $30	Hunger Satiety $50
Hormone Test $20	Hormone Test $30	Hormone Test $35	Hormone Test $40	Hormone Test $50
		MRI $45	MRI $50	MRI $50
		Endoscopy $70		
Weight Mgmt. (3 visits) $40	Weight Mgmt. (5 visits) $50	Weight Mgmt. (6 visits) $55	Weight Mgmt. (7 visits) $60	Weight Mgmt. (1 visit) $5
Blood Tests $10	Blood Tests $10	Blood Tests $10	Blood Tests $10	Blood Tests $15
Total $130	**Total $130**	**Total $255**	**Total $220**	**Total $210**

Subjects who meet the entrance criteria will provide informed consent before being enrolled into the study. Consent will be obtained at the first visit at the Weight Management Center or Interventional Radiology. Participants will have as much time as necessary for giving consent.

Participants will have the study processes and consent form explained in detail, and then will be given time to read through the consent form. Participants will not be allowed to sign the consent form without reading through it first. Participants will be given the consent form in private; and probed for any potential questions they may have. A copy of the signed informed consent will be maintained and available for review by the Sponsor and designated monitor.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

This study is being conducted under IDE G190208 utilizing an investigational device, BTG-001933, which is a radiopaque embolic bead 100-200 µm (Biocompatibles UK, Ltd) intended to be used for bariatric embolization of the left gastric and/or gastroepiploic arteries. The summary of test validation studies is on file with the FDA and available in the Investigator's Brochure.

Control Arm Procedures
Participants randomized to the control arm will follow the same screening and pre-procedure assessment, and will also take the same pre-procedure medications. After becoming eligible, participants will be scheduled for their procedure. On procedure day, the interventional radiologist will determine radial or groin access in the post-anesthesia care unit per local policy. After the participant and procedure area are prepped, and a basic tray is opened, all participants will be given standard moderate sedation medications. At this point, the participant will have a drape placed over a drape support above their face to limit their vision and be given ear plugs and noise-cancelling headphones to dampen their hearing, preventing them from seeing and hearing the procedure but still allowing them to keep in contact with the procedure team. The participant will be randomized to either the control or intervention arm using central randomization software. Participants randomized to the control arm will receive no other procedural intervention. The procedural team instead will follow a prescribed simulated protocol that will mimic an actual embolization procedure. All participants will receive subcutaneous lidocaine and a skin nick to their groin or their wrist as pre-determined by the operating physician in the pre-anesthesia care unit, including those randomized to the control arm. If the skin nick is on the wrist, the operating physician will close it with an external compression device, and if it is in the groin, the physician will hold pressure for at least 5 minutes.

All procedure images and reports, regardless of the randomization arm, will be kept with the unblinded member of the study team, and will not be housed centrally. All participants will adhere to the same follow-up schedule, meeting with blinded members of the study team only. The procedural team will not have further contact with the participant, the participant will only be followed by the blinded study team. Once the study is closed, all reports and images will be entered into the clinical record.

Bariatric Embolization Procedure
The bariatric embolization procedure will be performed under moderate sedation by experienced interventional radiologists. This procedure will take about one-and-a-half to three hours. The manufacturer's Instruction for Use will be followed for the procedure.

The participant will be placed on the X-ray fluoroscopy table. Radial or femoral vascular access will be achieved using a small 21-gauge needle, then dilated serially over a guidewire to accommodate a 5 French vascular sheath(23). The participant will receive local anesthesia in the skin of their leg or wrist, then a different small catheter will be placed through the participant's skin into an artery that leads to the participant's abdomen.

Using standard catheters, 3-dimensional imaging will be acquired of the stomach, the arteries supplying the fundus arising off the celiac vessel will be selected. Then, a microcatheter will be advanced into the left gastric and/or gastroepiploic arteries supplying the fundus and small calibrated spheres (100-200 µm size [BTG-001933]) will be infused until stasis of anterograde arterial flow is achieved, with particular care to avoid infusion of non-target arteries. Only the left gastric and/or gastroepiploic arteries will be embolized. Stasis will be defined as visualization of contrast within the target artery for at least 5 cardiac cycles.

Upon completion, repeat 3-dimensional imaging will be acquired to assess bead distribution and fundal coverage. Following this the catheters will be removed and hemostasis will be achieved with manual compression or a closure device.

The participant will be monitored in the post-sedation recovery room until the participant meets the usual admission criteria, per local policy, followed by an overnight hospital admission for observation. During observation, intravenous fluids will be given to ensure adequate hydration status. If necessary, participants will be given analgesics, anti-nausea, and anti-emetic medication. If the participant continues to display pain, nausea, vomiting, etc., the participant may be kept in hospital for up to 48 hours post-procedure. The participant will be asked to avoid exertion for 48 hours following the procedure. Participants will adhere to a written post procedure diet plan consisting of a slow advancement from clear liquids, progressing to full liquids and finally solids. At which point they will be advanced to a regular diet as directed by the Weight Management Center. Please see post procedure diet plan in Appendix A.

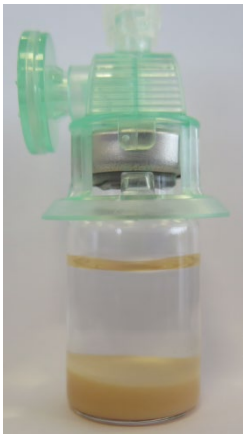
6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Inventory of the BTG-001933 product will be maintained by the study team in a secure location with dispensing records completed to document supply receipt, dispensation, and return of unused product.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The BTG-001933 product is provided by the manufacturer (Biocompatibles UK, Ltd) packaged as individual cartons containing one vial of product and one ViaLok Vented Vial Access Device (Yukon Medical LLC). The vial and carton are labeled For Investigational Use Only.



The primary packaging material of the vial includes:

Material	Description
10 ml glass vial	10ml ISO Clear Type I Glass Vial with 20mm Crimp Neck
Vial stopper	20 mm fluoropolymer film coated bromobutyl rubber Injection stopper 4023/50 Grey B2-40 Westar® RS
Flip-off tear-off crimp cap	Aluminum cap with a colored plastic (polypropylene) button seal Size 100 – 200µm: red

6.2.3 PRODUCT STORAGE AND STABILITY

Based on the evidence of 24 months shelf life for LC Bead LUMI™ and available 6 months real time and accelerated stability data for BTG-001933, an initial shelf life claim for the investigational device BTG-001933 for use in clinical studies of 18 months at 2 – 25°C has been defined. The shelf life will be extended based on the results of ongoing stability studies, if appropriate.

The following storage conditions are defined for BTG-001933:

- Unopened BTG-001933 must be stored between 2˚C to 25˚C, in a dry place in its original packaging. Protect the product from light.
- Use by the date indicated on the vial label.
- Do not freeze.

6.2.4 PREPARATION

The bead suspension of BTG-001933 in buffered saline is to be transferred from the vial into a 10 mL syringe by using the transfer device prior to administration to the patient. The transfer device is supplied with the product and is co-packaged in the device carton with the BTG-001933 vial. The transfer device (20 mm ViaLok Vented Vial Access Device (Yukon Medical LLC)) is a sterile medical device intended to access standard vials for needle-free preparation and administration. Details of product preparation are given in the manufacturer's Instruction for Use.

6.3 MEASURES TO MINIMIZE BIAS: SITE TRAINING RANDOMIZATION AND BLINDING

Of the 59 participants who will participate in this research, 27 participants will be randomized to the intervention arm, and 27 participants will be randomized to the control arm. The first 10 patients to meet all eligibility criteria will be the 10 pilot patients; these patients will not be analyzed with the randomized patients.

In this double-blind experiment, neither blinded study team nor participants will know the details of the participants' randomization. Unblinded members of the study team will perform the procedure and have access to the medical record in case of emergency. All study visits involving study intervention and the details of the procedure, including start/stop times, will be recorded on the relevant eCRF by the unblinded team member.

All participants will undergo the same preparation for the procedure, then, when the procedure begins, the participants will be blindfolded with a head drape and will have their hearing damped with ear plugs and noise-cancelling headphones, preventing them from seeing and hearing the procedure, but still allowing them to keep in contact with the procedure team. All procedure images and reports, regardless of the randomization arm, will be kept with the unblinded member of the study team, and will not be housed centrally. All participants will adhere to the same follow-up schedule, meeting with blinded members of the study team only. The procedural team will not have further contact with the participant, the participant will only be followed by the blinded study team.

After all subjects complete the follow-up period, the study team and the subjects will each complete a survey to determine to which arm they thought each subject was randomized. After the surveys are completed, both the investigator and subject will be unblinded at the same time. Once the study is closed all reports and images will be entered into the clinical record.

6.4 STUDY INTERVENTION COMPLIANCE

Embolization and device placement will be assessed by radiographic imaging.

Subject-completed logs recording diet, hunger levels, weight, and symptoms will be reviewed to determine compliance with the weight management intervention prior to the procedure and during the follow-up period.

6.5 CONCOMITANT THERAPY

The participant will be asked to take an oral proton pump inhibitor (Omeprazole 40 mg, daily) and an oral cytoprotective agent (Sucralfate 1 g, two times a day), which coats and protects the stomach lining for two weeks before and six weeks after the procedure to prevent stomach irritation. Participants suffering from diabetes will be asked to withhold their diabetes medication on the day of the procedure.

Daily NSAID use should be avoided to reduce the risk for peptic ulcer disease.

At every study visit, new medications or changes in concurrent medications on the appropriate concurrent medication eCRF will be recorded. Documentation will include dosage, start/stop dates and any drug holidays.

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

All decisions to stop the study in any subject, or the study as a whole, will be made by the DSMB, a multidisciplinary team. This team will include a gastroenterologist, psychologists, obesity specialist, bariatric surgeon, and interventional radiologists. If the DSMB decides to remove a subject, the investigator will refer the subject to necessary medical care for follow-up.

The DSMB will halt the study for evaluation and possible discontinuation if one or more subjects experience any of the following events:

- Gastric ulcerations which require endoscopic or surgical intervention
- Gastrointestinal bleeding that reduces hemoglobin >3 gm/dL
- Significant abdominal pain requiring hospitalization >48 hours post procedure
- Inability to retain ingested fluid or solid food >48 hours post procedure due to persistent nausea and vomiting
- Radiation overexposures
- Any other unexpected organ injury that could be related to the procedure including but not limited to the following: abdominal abscess, bowel infarction or perforation, hypoxemia, azotemia, heart failure, pulmonary venous congestion, shock, deep vein thrombosis, pulmonary emboli or death

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- For subjects who withdraw before the end of the study, all End of Study assessments should be completed, if possible, prior to withdrawal. All AEs must be documented in the patient medical notes and in the electronic case report form (eCRF).
- If a subject withdraws from the study for any reason, all efforts should be made to follow AEs unless the subject withdraws consent.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request.

The DSMB will determine if stopping rules apply. Stopping rules that would necessitate withdrawal of any individual subject include development of any of the following conditions during the six-month period following the procedure. All efforts should be made to follow AEs to resolution or stabilization unless the subject withdraws consent:

- Development of gastric ulceration observed at the follow-up endoscopy that requires surgical therapy. If ulceration can be managed medically, it will be treated by a gastroenterologist, and the participant will remain in the study.
- Small bowel obstruction, hernia, small bowel incarceration, abdominal abscess, gastrointestinal bleed, hypotension, new onset cardiac ectopy, bradycardia, tachycardia, bowel perforation, pneumothorax, pneumonia, hypoxemia, azotemia, heart failure, CO2 narcosis, ventricular bigeminy, pulmonary venous congestion, septicemia, shock, mesenteric venous thrombosis, deep vein thrombosis, pulmonary emboli, adhesions, or death.
- Subjects may also be removed from the study by the investigator for the following reasons:
    - Staying in the study would be harmful to the subject (this includes new pregnancy during follow-up).
    - The subject needs treatment that is not allowed in the study.
    - It is decided that another therapeutic approach can improve the subject's medical care.
    - The subject fails to follow instructions.
    - The subject is not complying with study visits.
    - The study is cancelled.
    - There may be other reasons to remove study subjects that are not known at this time.

The reason for participant discontinuation or withdrawal from the study will be recorded on the electronic Case Report Form (eCRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the final scheduled visit and is unable to be contacted by the study site staff. Attempts to contact will occur as below for all missed study visits.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit within ±3 days for the weekly visits and within ±2 weeks for monthly visits, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record and study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY PERIOD DEFINITIONS

Baseline & Screening Period
After initial eligibility is determined and informed consent is provided, participants will be assessed against all eligibility criteria over a two-month period. Initial lab results will be compared with repeat lab results obtained within 30 days of the embolization procedure to confirm eligibility. The signed consent form authorizes abstraction of existing data from a patient's medical chart for data collection. Participants will be screened by two physicians, an interventional radiologist, and an internist who specializes in obesity. Screening and baseline visits may be combined if patient and physician schedules will allow. The screening phase begins when the informed consent is fully signed and dated and ends at randomization. The PI may repeat any of the screening tests.

Pre-Procedure Period
This period begins after initial eligibility is determined during the Baseline & Screening Period and ends at randomization.

Procedure Day
This day is scheduled only after all eligibility criteria are satisfied during the previous periods.

Follow-Up Period
This period begins with day 1 post Procedure Day and ends at the final visit at month 12.

Participants will be in the study for up to two years after signing consent and 12 months post embolization. Participants may be followed clinically for up to five years per routine care after the end of the study. For their 12 months of follow up post-procedure, the participants will be asked to come to clinic visits at weeks 1 and 2, and months 1, 3, 6, and 12.

During each clinic visit the following may occur:

- Participants will be evaluated by a study team member, data and home logs will be recorded and collected, will undergo a targeted history and physical exam, and will be asked to fill out any needed questionnaires.
- When attending weight management visits, they will also be evaluated by an internist who specializes in weight management.
- Medication changes will be documented.
- Intensive medical therapy consisting of lifestyle counseling and weight management will be provided to all participants. Diabetic subjects will have their medications managed by a diabetes specialist, per routine care, as defined by American Diabetes Association

guidelines. Any changes in diabetes medication regimen will be documented in the electronic case report form. These data will be used to calculate a medication effect score (MES).
- Participants will be asked to eat nothing after midnight prior to their clinic visits.

8.2 STUDY ASSESSMENTS AND PROCEDURES DEFINITIONS

8.2.1 Informed Consent
See section 10.1.1 for a full description.

8.2.2 Demographics
The following demographic data will be obtained: date of birth/age, gender, child-bearing potential, race, ethnicity.

8.2.3 History & Physical
Medical history deemed clinically significant, relevant to the clinical trial objectives and design, will be collected per body system (allergy/immunology), auditory/ear, blood/bone marrow, cardiac arrhythmia, cardiac general, dermatology/skin), endocrine metabolic, gastrointestinal, hemorrhage/bleeding, hepatobiliary/pancreatic, infection, musculoskeletal/soft tissue, neurologic, ocular/vision, psychiatric, pulmonary/upper respiratory, renal/genitourinary, sexual reproductive function, vascular).

The use of concurrent medications (medications taken within 30 days of screening and during the conduct of the study) will be obtained and documented in source documentation and on the relevant eCRF.

All ongoing medical conditions and adverse events arising from treatment of those conditions present for 30 days or more are generally considered a part of the patient's baseline medical history and must be recorded where indicated.

A full physical examination, including actual measured height (required at screening only) and actual scale measured weight, will be performed by a qualified licensed individual. A review of body systems will include the following:
- Waist circumference
- General appearance, overall well-being and functional capacity
- Skin
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Respiratory
- Cardiovascular
- Abdomen (including liver, gastrointestinal system)
- Musculoskeletal, extremities and mobility
- Neurological
- Vital signs: Assessments of vital signs (e.g., blood pressure, heart rate, temperature) will be performed at all study visits. When possible, blood pressure and heart rate will be determined after the patient has been in the sitting position for 5 minutes. Respiratory rate will only be obtained at baseline (i.e. at the weight management intake visit during screening).

A full physical examination as detailed above will be performed at baseline (weight management screening intake visit), 1-week, 2-weeks, and 1-month post-procedure. Vital signs, including weight, will be taken at all visits with weight management, however, waist circumference will only be measured at the weight management intake visit (screening period), on procedure day, and at the 1-month, 3-month, 6-month, and 12-month post-procedure weight management follow-up visits.

Any abnormalities or changes in intensity, duration or frequency not noted during the initial review of body systems should be documented in the source documentation and reported appropriately in the eCRF. If a new clinically significant finding, or if a change occurs at subsequent visits, the new finding must be assessed for adverse event criteria and will be documented. Resolution of any abnormal findings reported during the study will be noted in the source documentation and the eCRF.

8.2.4 Psychological Evaluation

- **Before -** A psychological evaluation will be completed and scored prior to the first visit. A screening form will be used utilizing inclusion and exclusion criteria to avoid further unnecessary testing. The initial evaluation will be, on average, 1.5 hours.

After - Follow-up visits are usually 1 hour and will largely depend on the plan with the Johns Hopkins Healthful Eating, Activity & Weight Program and the degree to which the participant presents with psychopathology that requires follow-up. Participants will meet with the same study psychologist with whom they did their initial screening 2-4 weeks after the procedure, and develop a follow-up plan which will be adjusted to suit each individual participant's needs. At a minimum, this will include scheduled visits at 1, 3, 6, and 12 months; follow-up visits may be conducted more frequently than specified (i.e. optional 9-month visit) or completed remotely (i.e. telehealth) if clinically indicated—this will be at the discretion of the study psychologists.
The participant will follow up with the same psychologist who conducts the initial evaluation, except in urgent or emergency situations in which that psychologist is not available.

8.2.5 Blood, Urine, and Stool Tests

Blood tests including complete blood count, tests of liver and kidney function, serum albumin measurement, electrolytes, urea, creatinine measurements (EUC), and fasting chemistries, including glucose and insulin, will be performed at screening (and again before the procedure if the screening blood tests were done more than 30 days before the procedure) and every study visit thereafter (week 1, week 2, week 4, month 3, month 6, month 12).

A stool occult blood test to identify gastrointestinal bleeding and H. pylori blood antibody test to see if the participant has been exposed to a specific type of bacteria that can cause stomach ulcers will be performed only at screening.
All clinical laboratory assays will be performed at the Johns Hopkins CORE laboratory according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out of range pathological changes. Abnormal laboratory values which are unexpected or not explained by the patient's clinical condition should be repeated until confirmed, explained or resolved. Changes from screening will be recorded as an adverse event if clinically significant.

The following clinical laboratory assessments will be completed at specified study visits during the study.

Biochemistry
- Sodium
- Potassium
- Calcium
- Blood Urea Nitrogen
- Creatinine
- Albumin
- Total Protein
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Alkaline phosphatase (ALP)
- Total and indirect bilirubin
- Glucose
- Lactate Dehydrogenase (LDH)
- Insulin
- Pancreatic enzymes: Amylase and Lipase

Coagulation
- Prothrombin Time (PT)
- Partial Thromboplastin Time (PTT)
- International Normalized Ratio (INR)

Hematology
- Hemoglobin
- Hematocrit
- White Blood Cell (WBC) Count
- Platelet Count
- WBC Differential and ANC
- Red Blood Cell (RBC) Count
- Mean corpuscular volume (MCV)

Lipid Profile
- Low-Density Lipoprotein (LDL)
- High-Density Lipoprotein (HDL)
- Triglycerides
- Total Cholesterol
- Total Cholesterol: HDL Ratio
- Non-HDL Cholesterol

8.2.6 Pregnancy Test
A urine or serum beta hCG pregnancy test will be performed on all females of child-bearing potential as a part of the screening process. If the participant is a woman who is able to become pregnant, she will have a repeat pregnancy test on the day of or the day before the embolization procedure. The result of this test must be negative for her to continue in the study. Women of fertile age must agree to use birth control for the duration of the study. Pregnancy tests will also be performed within a week of endoscopies and nuclear medicine gastric emptying tests.

Pregnancy: any report of complications of pregnancy such as miscarriage or congenital abnormality recorded for any female study participant or female partner of a male study participant should be reported immediately as an SAE. Participants will be asked to use contraceptives for the duration of the study, but if they become pregnant during the study, the

participant will be removed from the study. Every effort should be made to gather information regarding the pregnancy outcome until 8 weeks post-partum. It is the responsibility of the Investigator to obtain all pregnancy information.

8.2.7 3D CTA

A 3D CT angiography will be done to check the celiac and gastric vasculature. We plan to embolize only the left gastric and/or gastroepiploic arteries.

8.2.8 Gastric Emptying

Subjects who suffer from diabetes will have a screening gastric emptying (gastric motility/emptying) scan. The result of this scan should be normal for the subject to be able to continue. After the embolization, should any participant present with symptoms of delayed gastric emptying, the PI will order another gastric emptying scan.

8.2.9 Endoscopy with Biopsy

An upper GI endoscopy, also known as esophagogastroduodenoscopy (EGD) will be done to determine any contraindication for the study and to determine the presence of ulceration or any other adverse event (AE).

The endoscopy is also done to determine the health of the GI tract pre- and post-embolization. During the endoscopy, a long, flexible, lighted tube, called an endoscope, is guided through the patient's mouth and throat, then through the esophagus, stomach, and duodenum. A video camera in the endoscope will be utilized to inspect organs and detect abnormalities. Pre-procedure and post-procedure biopsies will be obtained to look at hunger hormone (ghrelin) levels in the stomach. Specifically, the biopsy will be accomplished using a device that looks like a small alligator clip at the end of the endoscope which will close over a very small sample of stomach tissue and allow for its extraction. In the case that an ulcer, inflammation, or mass is noted on endoscopy, additional biopsies may also be taken for further analysis of those regions.

Endoscopic images will be described using standard clinical terms, which include size, location, and depth of observed ulceration. All endoscopy images will be recorded, archived, and reviewed by the same advanced endoscopist.

8.2.10 Quality of Life Questionnaires

A Quality of Life instrument suitable for the general population and patients being treated for obesity will be administered at study visits specified in the schedule of events.

The Impact of Weight on Quality of Life (IWQOL) questionnaire is the first questionnaire developed to specifically assess the effects of obesity on health-related quality of life. The psychometric properties of the IWQOL are excellent, but given its length, a briefer version was developed, the Impact of Weight on Quality of Life-Lite Questionnaire (IWQOL-Lite). The five identified scales (Physical Function, Self-Esteem, Sexual Life, Public Distress, and Work) and the Total score have demonstrated excellent reliability (0.90–0.94 for the scales, 0.96 for Total score), validity, and utility with various groups of obese individuals. In this chapter, the rationale for the development of an obese-specific quality of life measure will be briefly reviewed, followed by the background and development of the IWQOL and IWQOL-Lite (including their psychometric properties), weight loss research using these instruments, and future research directions. It is concluded that the IWQOL-Lite is a reliable, valid instrument that can be utilized in various obese populations, and may be particularly useful as a treatment outcome measure.

8.2.11 Hormone Tests
Fasting levels of obesity-related hormones will also be measured from patient's blood. These will include such hormones as ghrelin, LEAP2, GLP-1, PYY, CCK, leptin, etc.

8.2.13 MRI (with AMRA Profiler)
A semi-automated cloud-based image analysis tool, AMRA Profiler, optimizes MR images to fully analyze entire body compartments, and provide precise body composition measurements. AMRA Profiler uses quantitative fat and water separation to integrate the total fat signal intensity in a compartment of interest; and provide a three-dimensional approach to improve the robustness of the segmentation. This system is quick, cost effective, validated, and reproducible. The automated single scan computes multiple measurements, and is completed in six minutes using fewer coils, no radiation, or contrast. MRI scans with body composition analysis will be performed before the bariatric embolization procedure, and four times over 12 months after the procedure, at weeks 4, and months 3, 6, and 12. A standard 1.5T or 3T scanner with AMRA Profiler will be used to quantify visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (ASAT), thigh muscle volume, proton-density liver fat fraction, total adipose tissue volume (TAT), total lean tissue volume (TLT), muscle group volumes, intramuscular adipose tissue (IMAT), and individual muscle volumes. The data will be analyzed in conjunction with weight and HbA1c in order to see what patients will be suitable in the future for this procedure to determine which participants are suited and will benefit most from this procedure. As possible characterization of fat will be performed. In addition to the MRI with AMRA Profiler, the scan will also include Siemens work-in-progress sequences for evaluating fatty acid composition. Overall, the MRI is expected to take 30-38 min per session.

8.2.14 Weight Management Counseling
- **Before –** Following consent, the participant will have a total of eight visits over the 2-month screening period with the weight management team at the Johns Hopkins Greenspring Campus Healthful Eating, Activity & Weight Program. This will include an initial 1-hour intake with a physician, consisting of a detailed review of medical history and a physical exam, followed by 7 weekly 15-minute meetings with either a physician as follow-up or other medical staff for weight checks. After their intake visit, reasonable, controlled diet plan will be outlined for the participant. Some visits may occur using a secured telemedicine link (see supplemental form).

After – The first two months after the procedure, participants will have weekly visits with the Johns Hopkins Healthful Eating, Activity & Weight Program (HEAWP), alternating between visiting with a HEAWP physician and a weight check each week. In months 3 to 5, they will have a visit with a HEAWP physician every other week (i.e. two visits a month). In month 6, they will have one visit with a HEAWP physician and one visit with other medical staff at the clinic for a weight check. Lastly, from month 7 to 12, they will only have monthly visits with a HEAWP physician. Each follow-up visit should take around 15 minutes.

8.2.15 Randomization
Data documenting demographic information, medical history, physical examination, medication and prior treatment, clinical labs, pregnancy test, and urinalysis will be reviewed against the eligibility criteria to determine eligibility. The determination will be recorded on the relevant eCRF.

If a patient is determined to be eligible to participate in the study, the patient will be randomized.

Randomization will be determined using assignment by a computer-generated randomization scheme. Upon randomization/enrolment, each patient will be assigned a unique numeric patient identity code.

8.2.16 Bariatric Embolization/Sham Procedure
See section 6.1.1.

8.2.17 CT
Upon completion of the embolization procedure, a CT scan will be acquired to assess bead distribution and fundal coverage.

8.2.18 Assessment of AEs
Patients will be required to report adverse events spontaneously. At every study visit, staff will ask general, open-ended, non-directed questions to obtain information about AEs. If the patient is unable to attend a study visit, AEs can be collected by telephone contact.

At any time during the study, the patient may volunteer information that resembles an AE. The Investigator should obtain all the information required to complete the AE form. Where possible, a diagnosis, rather than a list of signs or symptoms, should be recorded. Any medical management of an event and the resolution of an event must be recorded in source documentation and on the appropriate eCRF using medical terminology according to Sponsor instructions.

The Investigator will assess all AEs for grading, severity and relationship to study treatment(s) and/or procedure(s). Definitions and procedures for assessment can be found in Section 8.3.

8.2.19 Food Logs, Eating Behaviors, and Taste Preferences
- The food log component of our study involves two factors: Lose It! food tracking and the ASA24 questionnaire. The **Lose It! food log** will be used for intervention purposes as well as general data tracking, as participants will be asked to fill it out on a daily basis, while the **ASA24** will be used to obtain more standardized information regarding the subject's eating behavior, and will be conducted over the phone at the specified timepoints in the study calendar.

8.2.20 Hunger Satiety Scale
This scale is a 6-day appetite evaluation that will be collected at the specified timepoints in the study calendar.

8.2.21 HealthReel
The HealthReel app will be used by patients to measure and track changes in their body composition throughout the study.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Definition of Adverse Events (AE) and Adverse Device Effects (ADE)

Adverse event (AE) means any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device.
An adverse device effect (ADE) is an AE, as previously defined, related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational device. This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

8.3.1 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE) AND SERIOUS ADVERSE DEVICE EFFECTS (SADE)

A serious adverse event (SAE) is an adverse event that:

a) Led to a death, injury or permanent impairment to a body structure or a body function.
b) Led to a serious deterioration in health of the subjects, that either resulted in:
    a. A life-threatening illness or injury, or
    b. A permanent impairment of a body structure or a body function, or
    c. In-patient hospitalization or prolongation of existing hospitalization, or
    d. In medical or surgical intervention to prevent life threatening illness.
c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.

A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a SAE, as previously defined.

An unanticipated serious adverse device effect (USADE) is a serious adverse device effect, which by its nature, incidence, severity or outcome has not been identified in the current version of the protocol or Investigator's Brochure. This includes unanticipated procedure-related serious adverse events; that is serious adverse events occurring during the study procedure that are unrelated to any malfunction or misuse of the investigational medical device.

8.3.2 CLASSIFICATION OF AN ADVERSE EVENT

8.3.2.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities. (Equivalent to Grade 1 events if using CTCAE reporting)
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning. (Equivalent to Grade 2 and 3 events if using CTCAE reporting)
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious". (Equivalent to Grade 4 events if using CTCAE reporting)

8.3.2.2 RELATIONSHIP TO STUDY PROCEDURE

All adverse events (AEs) must have their relationship to investigational device and/or procedure assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the investigational device and/or procedure). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

An AE becomes an ADE when the AE is considered if the attribution is possibly, probably or definitely related associated with the use of the test device.

8.3.2.3 EXPECTEDNESS

The investigator will be responsible for determining whether an AE is expected or unexpected based on the device labelling and Investigator Brochure. An AE will be considered an unanticipated adverse device effect (UADE) if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the investigational device and/or procedure.

8.3.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. In this study, patients should be encouraged to report AEs spontaneously or in response to general, non-directed questions.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event

description, time of onset, clinician's assessment of severity, relationship to investigational device and/or procedure (assessed only by those with the training and authority to make a diagnosis), and date and time of outcome of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution or stability.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator or designee will record all reportable AEs (includes AE, ADE, SAE, SADE, UADE) with start dates occurring any time after exposure to the investigational device. An AE occurring after informed consent and prior to exposure of the investigational device will be added to the subject's history. All AEs will be collected through the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.4 ADVERSE EFFECT REPORTING

Adverse events will be recorded on the AE eCRF. The Investigator or physician sub-Investigator will judge the severity of each AE and whether or not it is treatment-related. All AEs that occur after signing of informed consent including events likely to be related to the underlying disease or likely to represent concurrent illness, will be reported, including events present at Baseline which worsened during the study.

The Investigator will be responsible for informing the IRB and reporting annually to the FDA as outlined in 21 CFR 812.

8.3.5 SERIOUS ADVERSE EFFECT REPORTING

Any SAE, SADE or UADE must be reported by telephone or fax to the Sponsor or it's designate as specified in the study procedures within 24 hours of learning of the event. In the event of an emergency, the Investigator will contact the Sponsor safety officer using the coordinates specified in the study procedures manual.

Each AE reported on an SAE form must also be reported in the AE section of the eCRF.

The study investigator shall complete the SAE eCRF and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The entire SAE form needs to be completed, if possible, to keep requests for additional information to a minimum. Patients experiencing SAE, SADE or UADE should be followed clinically and with laboratory studies, if appropriate, until medical treatment and/or medical monitoring of the event is no longer required because the event resolves or stabilizes, returns to baseline if a baseline value is available, can

be attributed to agents other than the study treatments or a referral for appropriate follow-up care has been made.

The Principal Investigator, who is also the study sponsor for this study, is responsible for conducting an evaluation of a UADE and shall report the results of such evaluation to the Food and Drug Administration (FDA) in accordance with 21 CFR 812 and to the reviewing IRB within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.6 REPORTING EVENTS TO PARTICIPANTS

Participants will be informed of any new information that may affect their decision to continue participation after IRB approval.

8.3.7 REPORTING OF ADVERSE EVENTS TO THE MANUFACTURER

All SAEs and UADEs will be reported to BTG within 24 hours of becoming aware of the event by emailing a copy of the CRF to *Vigilance@btgplc.com* The Investigator/Sponsor is responsible for obtaining any data BTG requires to complete the investigation of the event.

A full listing of non-serious AEs will be provided to BTG at the conclusion of the study.

8.3.8 REPORTING OF PREGNANCY

Any report of pregnancy or complications of pregnancy such as miscarriage or congenital abnormality recorded for any female study participant or female partner of a male study participant should be reported immediately as an SAE. Participants will be asked to use contraceptives for the duration of the study, but if they become pregnant during the study, the participant will be removed from the study. Every effort should be made to gather information regarding the pregnancy outcome until 8 weeks post-partum. It is the responsibility of the Investigator to obtain all pregnancy information.

Reporting procedures for SAE will be followed as outlined in section 8.3.6.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An UP could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (Ups) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 10 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 days of the IRB's receipt of the report of the problem from the investigator.]

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)). A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan will be a separate document and will be updated as required, in association with any protocol amendments. The plan will include descriptions of tables, listings and figures and will describe statistical programming considerations.

9.1 STATISTICAL HYPOTHESES

Statistical hypothesis:

The mean weight loss from baseline at 12-months post-randomization in the BAE arm will be statistically significantly (2-sided p-value <0.2) greater than in the sham arm. Since this is a phase 2 study, it is appropriate to use a two-sided p-value greater than the standard 0.05 value (see below).

9.2 SAMPLE SIZE DETERMINATION

Sample sizes per randomized treatment arm for the proposed study are based on providing sufficient power for testing the primary hypothesis that BAE leads to larger mean weight loss from baseline than a sham procedure.

Based on previous data, it is anticipated that the mean weight loss from baseline at 12-months post-randomization in the BAE arm will be at least 8 kg.(21, 36, 37) In contrast, we expect that participants in the sham arm will lose 3.3 kg at 12 months (corresponding to 3% weight loss from a baseline weight of 110 kg). Also, a common standard deviation for the change in weight from baseline at 12 months of 7 kg is assumed based on the data from the prior BEAT Obesity trial. Using a two-sample t-test and a two-sided alpha of 0.2, 21 participants in each arm will provide 80% power. The sample size is increased to 27 participants in each arm (i.e. a total of 54 randomized participants) to take account of an expected 20% drop-out rate by the time of the 12-month assessment. Since this is a phase 2 study, it is appropriate to use a two-sided alpha greater than the standard 0.05 value.

9.3 POPULATIONS FOR ANALYSES

Statistical analyses will follow the intent-to-treat paradigm, meaning all participants will be analyzed according to the treatment group to which they were randomized. However, we will also perform an analysis according to a modified intention-to-treat (mITT) paradigm. As defined here, mITT means that all participants will be analyzed based on the treatment arm to which they were randomized, provided that they had exposure to the treatment protocol in their assigned arm. Participants who are randomized to a particular treatment arm, but who do not receive exposure to this treatment will be considered as ‘mis-randomized’, and will not be included in the mITT population. Reasons for participant mis-randomization include: 1) discovering post-randomization that a given participant does not meet the inclusion / exclusion criteria and is subsequently withdrawn from the study, 2) a participant refuses treatment after randomization, 3) a clinical investigator refuses to treat a participant post-randomization according to the protocol for the treatment arm to which the participant was assigned for any reason, and 4) the participant withdraws from the study post-randomization, but prior to receiving exposure to study treatment, for any reason.

The ten pilot participants recruited in the proposed trial will not be analyzed with the participants recruited through randomization. Rather, these ten pilot participants will be used to test and refine the trial protocol, and data collection procedures.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

As a first step, descriptive statistics will be performed, and the normality of continuous variables evaluated using the Shapiro-Wilk test and through exploratory plots (e.g. histograms and Q-Q plots). Non-normal variables will be transformed to normality, using appropriate data transformations, or will be analyzed using non-parametric statistical methods. Frequency distributions, tabulations, and bar charts will be created to quantify categorical and binary variables. These exploratory analyses will help us assess data distributions, and also help identify any unusual, outlying or suspect observations. Next, initial confirmatory analyses will be used to determine whether there are significant differences in baseline demographic and clinical

variables between treatment arms, as well as between any comparable outside groups. These confirmatory analyses will include t-tests for continuous variables deemed to be normally distributed, or the non-parametric Wilcoxon Rank Sum test for non-normally distributed continuous variables. Binary and categorical variables will be analyzed using the Chi-Square goodness-of-fit test, or the Fisher's Exact Test, appropriate for categorical variables with small cell sizes. A lack of differences between treatment arms will be considered as evidence of adequate randomization; however, we expect that some baseline covariates will be imbalanced by treatment arm, given the small size of this study, due to chance.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy outcome for the proposed trial is total weight loss from baseline weight at 12-months post-randomization. Differences in the weight loss from baseline between the treatment arms will be compared using the two-sample t-test. In addition, we will also consider an ANCOVA model that looks at the group difference in mean weight loss from baseline, adjusting for baseline covariates that might be imbalanced by treatment arm.

Missing Data: As described above, we will be developing protocols to maximize follow-up. Our overall approach is to engage participants early on and keep them engaged through personal contact with the local center and access to information and resources that are relevant to them, their injury and their treatment. Furthermore, we do not expect the rates of missing data will be differential across treatment groups. As with most prospective studies, missing data will be unavoidable (even with excellent follow- up). Since the informative nature of missing data cannot be verified from the observed data, we will adopt a sensitivity analysis framework for reporting results. We will analyze data under a variety of modeling assumptions regarding how strongly the missingness mechanism is related to outcomes (see Rotnitzky, A, Scharfstein, DO, Su, TL, Robins, JM (2001). "Methods for conducting sensitivity analysis of trials with potentially non-ignorable competing causes of censoring." *Biometrics*, 57: 103-112).

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary outcomes include:

1) Change in body weight at timepoints other than 12 months
2) Percentage change in body weight
3) Achievement of a >5% reduction in body weight
4) Percentage of excess weight loss (EWL)
5) Change in multi-compartment body fat composition as measured by MRI

Differences by treatment arm in the proportion of participants with >5% weight loss will be statistically compared using the Chi-square goodness-of-fit-test. Risk differences and relative risks, along with corresponding 95% confidence intervals, will be calculated to quantify group differences in this endpoint.

9.4.4 SAFETY ANALYSES

The primary safety endpoint will be the differences in adverse events at 12 months post procedure. The statistical analysis on the secondary outcome for safety will consider differences in the adverse events (AEs) at 30-days post-procedure.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The BAE and sham groups will be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics such as mean, median, inter-quartile range, absolute values and percentages.

9.4.6 PLANNED INTERIM ANALYSES

An interim analysis of safety and technical utility of the embolic device (image visibility) and procedural assessments such as blinding, will be done after the 10 pilot patients complete the embolization procedure. Study reports on device/ procedure related complications are to be sent to the FDA following treatment of the ten (10) pilot patients and then after every 10 additional subjects are randomized and treated (blinded).

No interim analysis for efficacy or futility are planned.

9.4.7 SUB-GROUP ANALYSES

All primary, secondary, and safety analyses will be performed by gender, race, and ethnicity to determine if the treatment effect or safety differs by these demographics. Patient-specific clinical or “severity” factors/categories and treatment categories will be explored. Planned explorations include diabetic status, age, compliance with weight management, baseline ghrelin levels, and post-procedure imaging characteristics.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed. Only aggregate data will be reviewed.

9.4.9 EXPLORATORY ANALYSES

Several tertiary endpoints will be considered in the proposed trial as stated before including blood pressure values, lipid profiles, serum obesity hormones, food intake, hunger assessments, QoL measures, and changes in taste perception. These endpoints will be quantified using a variety of assessment tools with both continuous and categorical scores. Statistical differences by treatment in these assessments will include the two-sample t-tests for continuous scores that are normally distributed, or the non-parametric Wilcoxon Rank Sum test for non-normally distributed continuous scores, while the binary and categorical scores will be analyzed using the Chi-Square goodness-of-fit test.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 INFORMED CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION (21 CFR 50)

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB) and FDA-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI), who is also the sponsor for this trial, will promptly inform study participants, the Institutional Review Board (IRB), the FDA, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the DSMB (see section 10.1.6), sponsor, IRB and/or Food and Drug Administration (FDA). The FDA will be notified within 30 working days of the completion or termination of the investigation and submit a final report to the FDA and IRB within 6 months after completion or termination.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. Abstraction of existing data from a patient's medical chart during prescreening will be done under an IRB approved HIPAA waiver.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Johns Hopkins University, Division of Brain Injury Outcomes (an academic research organization). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Johns Hopkins University research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Johns Hopkins University.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Johns Hopkins University. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Johns Hopkins University, for use by other researchers including those outside of the study. Permission to transmit data to the Johns Hopkins University will be included in the informed consent.

When the study is completed, access to study data will be provided through the Johns Hopkins University.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor (TBD)**
Clifford Weiss, MD Professor, Interventional Radiology	Name, degree, title
Johns Hopkins University	Institution Name
1800 Orleans Street,	Address

Zayed Towers 7203	
(410) 614-1046	Phone Number
cweiss@jhmi.edu	Email

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including a gastroenterologist, bariatric surgeon, endocrinologist, and an interventional radiologist.

Members of the DSMB will be independent from the study conduct and free of conflict of interest, with measures in place to minimize perceived conflict of interest. The DSMB will meet at least semi-annually to assess safety data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the IDE Sponsor.

The DSMB will meet initially to set up and review protocol, after first 5 (non-randomized) participants have been embolized, after the first 20 randomized participants have undergone embolization or sham, and after the first 40 participants have undergone embolization or sham and after all 59 participants have undergone embolization or sham. The last DSMB meeting will occur 6 months after the last participant has been embolized, in addition to any meetings regarding any specific event. In addition, study reports on device/procedure related complications will be sent to the DSMB and FDA following treatment of the ten (10) pilot patients and then after every 10 additional subjects are randomized and treated (blinded). All meetings will be documented and any problems regarding the study protocol will be immediately relayed to the IRB and FDA. The principal investigator will be responsible for communicating all reports and events to the IRB.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council for Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by an independent academic research organization (ARO; Johns Hopkins University, Division of Brain Injury Outcomes, Baltimore, MD.
- Remote, risk-based, monitoring will be employed for 100% data verification of endpoint, safety and other key data variables. On-site monitoring visits will be employed early, for initial assessment and training and then for-cause as needed.
- The investigator and IDE Sponsor will be provided copies of monitoring reports within 7 days of visit.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the VISION EDC system (Prelude Dynamics, Austin, TX), a 21 CFR Part 11-compliant data capture system provided by the Data Coordinating Center (Brain Injury Outcomes (BIOS) Division of Johns Hopkins University). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Council on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention.

No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the Data Coordinating Center via entry into the eCRF. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

The funder (Biocompatibles UK Ltd.) will review the primary results manuscript prior to publication.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

None.

10.3 ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ANCOVA	Analysis of Covariance
ASA	American Surgical Association
ASAT	Abdominal Subcutaneous Adipose Tissue
BAE	Bariatric Embolization
BEATLES	Bariatric Embolization of ArTeries with imaging visible EmbolicS
BES	Binge Eating Scale
BIS/BAS	Behavioral Avoidance/Inhibition Scales
BMI	Body Mass Index
BP	Blood Pressure
CBCT	Cone Beam Computed Tomography
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CO2	Carbon Dioxide
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CT	Computed Tomography
CTA	Computed Tomography Angiogram
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DNA	Genetic Material
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EGD	Esophagogastroduodenoscopy
EUC	Electrolytes Urea and Creatinine
EWL	Excess Weight Loss
FCI	Food-Craving Inventory
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
GHS	Growth Hormone Secretagogue
GHS-R	Growth Hormone Secretagogue Receptor
GI	Gastrointestinal
GLP	Good Laboratory Practices
GLP-1	Glucagon-Like Peptide
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HEENT	Head, Ears, Eyes, Nose, Throat
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IMAT	Intramuscular Adipose Tissue
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization

ITT	Intention-To-Treat
IWQOL	Impact of Weight on Quality of Life
LB	Pounds
LEAP2	Liver-Expressed Antimicrobial Peptide 2
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MES	Medical Effect Score
MITT	Modified Intention to Treat
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NTE	Non Target Vascular Embolization
OHRP	Office for Human Research Protections
PI	Principal Investigator
PYY	Peptide YY
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
RYGBP	Roux-en-Y Gastric Bypass
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
T	Temperature
TAT	Total Adipose Tissue
TFEQ	Three-Factor Eating Questionnaire
TLT	Total Lean Tissue
UP	Unanticipated Problem
US	United States
VAT	Visceral Adipose Tissue

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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Appendix A: Post-Procedure Diet Plan (1 week)

Clear liquid diet (1-2 days)

A clear liquid diet consists of clear liquids — such as water, broth and plain gelatin — that are easily digested and leave no undigested residue in your intestinal tract.
Clear liquids and foods may be colored so long as you are able to see through them. Foods can be considered liquid if they are even partly liquid at room temperature. You can't eat solid food while on a clear liquid diet.

The following foods are allowed in a clear liquid diet:

- Water (plain, carbonated or flavored)
- Fruit juices without pulp, such as apple or white grape
- Fruit-flavored beverages, such as fruit punch or lemonade
- Carbonated drinks, including dark sodas (cola and root beer)
- Gelatin
- Tea or coffee without milk or cream
- Strained tomato or vegetable juice
- Sports drinks
- Clear, fat-free broth (bouillon or consomme)
- Honey or sugar
- Hard candy, such as lemon drops or peppermint rounds
- Ice pops without milk, bits of fruit, seeds or nuts

Any foods not on the above list should be avoided.

Once you can tolerate your clear liquid diet – you may progress to a:

Full liquid diet (1-2 days)

A full liquid diet is similar to a clear liquid diet, but you can also consume milk, vegetable juice, pureed soups and strained cooked cereals thinned with milk or water. Artificial sweeteners and liquid sweeteners are also allowed on a full liquid diet.

Foods Allowed on the Full Liquid Diet

- All kinds of fruits and vegetable juice
- Pureed fruit or vegetables
- Milk
- Soy or almond milk
- Yogurt (without fruit chunks)
- Melted cheese
- Eggs can be eaten as a soft custard
- Honey
- Syrup
- Coffee
- Tea
- Soft drinks
- Sports drinks
- Water
- Strained cooked cereal
- Broth
- Creamed soup (no pieces or chunks of vegetables or meats)
- Pureed meat can be added to soup (again, no chunks)
- Sugar
- Flavored gelatin
- Ice cream (no fruit, chocolate chips, etc.)
- Sorbet and frozen yogurt

Once you can tolerate your full liquid diet – you may progress to a:

Regular Diet as directed by the Weight Management Center

Once you advance to a regular weight loss diet, please avoid all sugary beverages – substitute with diet or sugar-free drinks. If in doubt – go with water!