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Title: Phase II Trial of Liraglutide (Saxenda(R), Novo Nordisk) in Adolescents with Obesity After Sleeve Gastrectomy: A Pilot Open-Label Study

Principal Investigator: Jack A. Yanovski, MD, PhD

Lead Associate Investigator: Anna Zenno, MD

NIH Principal Investigator: Jack A. Yanovski, MD, PhD

SGO/DEMGEO/DIR, NICHD
10 Center Dr, Building 10, Rm 1-3330, MSC 1103
Bethesda, MD 20892-1103
Phone: 301-496-0858
Fax: 301-480-4271
E-mail: jy15i@nih.gov

Investigational Agents *(if applicable)***:**

Drug Name:	Saxenda®
IND Number:	Exempt - PIND 154663
Sponsor:	NICHD
Manufacturer:	Novo Nordisk A/S

This project is a multi-institutional protocol with NIH and Children's National Hospital (CNH). The NIH IC is the Coordinating Center and Sponsor. John Perreault in the OCD will be the Clinical Safety Officer for this trial.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials 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 Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Phase II Trial of Liraglutide (Saxenda®, Novo Nordisk) in Adolescents with Obesity After Sleeve Gastrectomy: A Pilot Open-Label Study
Study Description:	This trial is an open-label Phase II non-randomized pilot study conducted at the NIH Clinical Center to investigate the efficacy of daily subcutaneous injection of liraglutide, a glucagon-like peptide-1 (GLP1) analogue to promote reduction of body mass index (BMI) in adolescents who continue to have obesity (BMI ≥30 or BMI ≥95th percentile for age and sex) 1 year or more after vertical sleeve gastrectomy (SG). We hypothesize that administration of liraglutide will be associated with reduction in BMI in such adolescents.
Objectives:	**Primary objective:** To determine the effect size for the change in BMI of liraglutide 3.0 mg daily subcutaneously at 16 weeks in adolescents who have obesity after SG, in order to use the observed changes to determine the sample size of a subsequent randomized, controlled investigation. **Hypothesis:** The Primary Endpoint is estimation of required sample size for a later randomized controlled trial through calculation of effect size for change in body mass index (BMI) from baseline to 16 weeks of liraglutide. The hypothesis is: The data will be sufficient to calculate the effect size for change in BMI from baseline to 16 weeks for a 2-group experiment (placebo versus liraglutide). **Secondary objectives:** To study the effects of 16 weeks of liraglutide 3.0 mg subcutaneously on change in mean BMI and fat mass in adolescents who underwent vertical sleeve gastrectomy (SG) ≥1y prior to study initiation but still have obesity or have a recrudescence of obesity despite surgery. To compare the effects of liraglutide on BMI and fat mass in enrolled participants who had a poor initial response to SG (<20% BMI reduction at BMI nadir) vs. those with a typical post-SG weight loss (≥20% BMI reduction at BMI nadir). **Additional Objectives:** To examine the effects of daily subcutaneous liraglutide in enrolled participants on changes in body composition, metabolic syndrome markers, energy intake, glucose tolerance, gastrointestinal (GI) hormone concentrations, appetite, free living physical activity, mood,

suicidality, weight related quality of life, self-perception of body image, and secretome.

Endpoints:

Primary Endpoint: Estimation of required sample size for a later RCT through calculation of effect size for change in body mass index (BMI) from baseline to 16 weeks of liraglutide.

Key Secondary Endpoints:

Changes in BMI and fat mass after 16 weeks of liraglutide

Comparison of changes in BMI and fat mass after 16 weeks of liraglutide in participants who had a poor initial response to SG (<20% BMI reduction at BMI nadir) vs. those with a typical post-SG weight loss (≥20% BMI reduction at BMI nadir)

Tolerability and safety of liraglutide 3.0 mg.

Additional (exploratory) Endpoints: Change from baseline to 16 weeks of liraglutide in:

1. Proportion reducing BMI by at least 5% and 10%
2. BMI standard deviation score for age and sex (BMIz)
3. Body weight
4. Percentage total body fat mass by DXA
5. Appetite score using visual analog scale (VAS)
6. Attention bias to highly palatable images
7. Energy intake at buffet meal
8. Free living physical activity by accelerometry
9. Metabolic syndrome markers (waist circumference, systolic and diastolic blood pressure, lipids, fasting plasma glucose level)
10. Fasting plasma insulin and HOMA-IR index
11. 2-hour oral glucose tolerance test (OGTT) insulin and glucose measurements
12. Hemoglobin A1C
13. Plasma GI hormones (GLP-1 and PYY) during OGTT
14. Weight related quality of life (QoL) score
15. Beck Depression Inventory total score
16. Body-Esteem Scale Score for Adolescents and Adults
17. Columbia Suicide Severity Rating Scale
18. Secretome analysis
19. Stool microbiome analysis

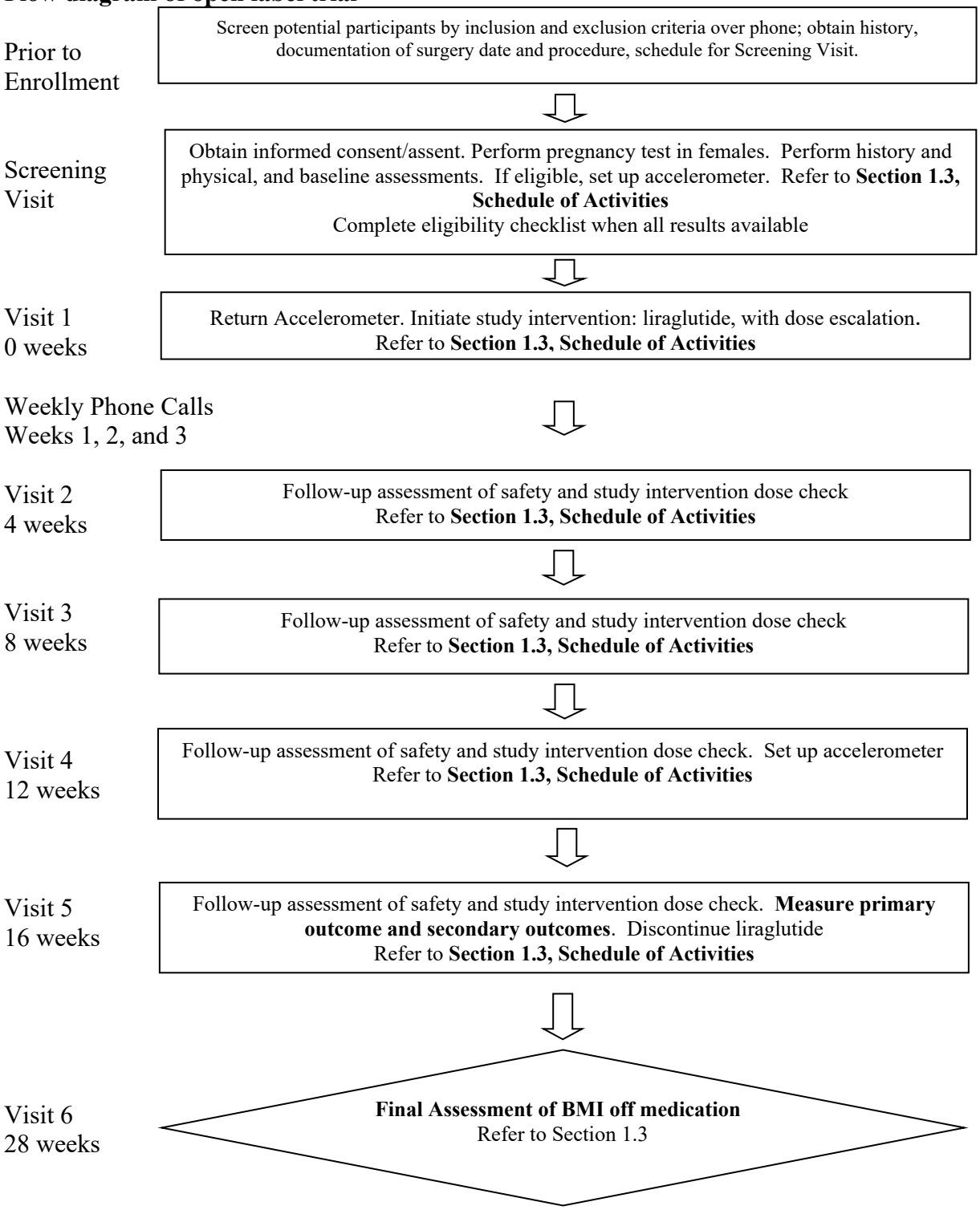
Study Population:

Up to a total of 50 male and female adolescents age <21 years old from Washington D.C., Maryland, and Virginia who underwent SG at least 1 year prior to enrollment and have BMI ≥30 kg or ≥95th

	percentile for age and sex in order to enroll at least 40 who are eligible and agree to take liraglutide for 16 weeks.
Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	We will primarily recruit participants who previously underwent SG from Children's National Hospital (CNH), in Washington, DC, a high-volume pediatric bariatric surgery center in our area. Participants will be assessed at the NIH Clinical Center for all study visits. Eligible participants may also be interviewed by telephone.
Description of Study Intervention:	Eligible patients will be treated with daily subcutaneous liraglutide (starting at 0.6 mg daily with weekly dose escalations up to 3.0 mg per day or max tolerated dose) for up to 16 weeks.
Study Duration:	36 months
Participant Duration:	7 months (28 weeks) (16 weeks on Study Drug and 12 weeks off Study Drug)

1.2 SCHEMA

Flow diagram of open label trial



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Phone Screen - ≤4 wks before baseline	Screening Visit	Study Visit 1 Day 0	Study Visit 2 Day 28 +/- 10 days	Study Visit 3 Day 56+/-10 days	Study Visit 4 Day 84 +/- 10 days	Study Visit 5 Day 112 +/-10 days	Final Study Visit 6 Day 196+/- 10 days
Informed consent		X						
Demographics	X	X						
Medical history	X	X						
Nutrition Counselling[1]		X	X	X	X	X	X	
Injection Teaching			X					
Administer study intervention[2]			X----------	----------	----------	----------	----------X	
Concomitant medication review	X	X----------	----------	----------	----------	----------	----------X	
Physical exam (including height and weight)[3]		X	X	X	X	X	X	X
Waist circumference[4]			X				X	X
Vital signs[5]		X	X	X	X	X	X	X
Pregnancy test [6]		X	X	X	X	X	X	
Screening labs (CBC, A1C, acute care panel, hepatic panel, mineral panel, ESR, CRP, 25-OH vitamin D, PT, PTT, urinalysis)		X						
Adverse event review and evaluation			X----------	----------	----------	----------	----------	----------X
DXA			X				X	
Metabolic syndrome markers[7]			X				X	
2-hour Oral glucose tolerance test (OGTT)			X				X	
Blood draw (Hb A1C, Plasma GI hormones: GLP-1, PYY, research samples to be saved)			X				X	
Stool sample collection (optional)			X				X	
Energy intake at buffet meal			X				X	
Appetite score pre and post meal using visual analog scale (VAS)			X				X	
Attention bias to palatable images study		X				X		
Free living physical activity by accelerometry set -up		X				X		
Weight related quality of life (QoL) score			X				X	
Beck Depression Inventory			X				X	
Columbia Suicide Severity Rating Scale			X				X	
Body-Esteem Scale			X				X	
Blood Sample for Secretome Analysis			X				X	

Complete Case Report Forms (CRFs)		X	X	X	X	X	X	X

1. Participants will meet with Nutrition Staff from the NIH Clinical Center to review instructions on keeping a log of their dietary intake at the Screening Visit, to review the intake log at Study Visits 1 and 5, and to receive standard obesity lifestyle management advice at Study Visits 1, 2, 3, 4, and 5.
2. First dose of liraglutide administered at the end of the visit after injection teaching.
3. Interim medical history for changes in health and limited symptom-directed physical examination, including injection sites at visits 2 through 5.
4. Waist circumference measured by Clinical Center Nutrition Staff.
5. Systolic and diastolic blood pressure measured after 5 minutes of rest.
6. Serum or urine pregnancy test (only for women of childbearing potential).
7. Fasting total, HDL- and LDL-cholesterol, triglycerides, fasting plasma glucose concentration

Summary Description:

Prior to Enrollment: The protocol will be explained to the participant and their parent (if the subject is <18 years of age). Research team will preliminarily determine participant's eligibility by inclusion and exclusion criteria over the phone.

Screening Visit: We will obtain informed assent and consent from the participant and their parent/guardian before initiating any research procedures. Each participant will undergo a history and physical examination (measuring weight, height, and blood pressure), and have screening labs drawn, and testing on attention bias to highly palatable images. Female participants will undergo a pregnancy test. Each participant will also answer a series of questionnaires, meet with Nutrition Staff from the NIH Clinical Center to review instructions on keeping a log of their dietary intake, and undergo set-up of a wrist accelerometer to measure free living physical activity. They will also receive material to collect stool at home if they choose to turn in stool samples at Visit 1.

Visit 1:

Each participant will undergo a brief history and directed physical examination at the NIH Clinical Center. Female participants will undergo a pregnancy test. They will then have fasting blood work followed by oral glucose tolerance testing (OGTT), DXA scan, appetite testing, and energy intake measurement at a lunch buffet meal at the NIH Clinical Center. Each participant will have the option to turn in stool samples collected at home or during their clinic visit. They will meet with Nutrition Staff to review their food log, receive standardized education on a healthy diet and physical activity, and measure their waist circumference. The wrist accelerometer will be returned. The participants will receive teaching on administration of subcutaneous study medication and receive their first dose at the end of Visit 1.

Phone Calls 1-3: Each participant will receive three weekly phone calls between Visit 1 and Visit 2 to discuss side effects and dose titration of study drug.

Visits 2-4: Each participant will undergo a brief history and directed physical examination to include injection site examination at monthly visits. Weight, height, and blood pressure will be measured at each visit. All participants will be assessed for adverse effects of study drug. Female participants will undergo a repeat pregnancy test at every visit. All participants will meet with Nutrition Staff to receive standardized education on a healthy diet. Used 1-month supply of liraglutide pens will be returned to research team and new 1-month supply of liraglutide will be provided to participant. At visit 4, a wrist accelerometer to measure free living physical activity will be placed and testing on attention bias to highly palatable images will be conducted. They will also receive material to collect stool at home if they choose to turn in stool samples at Visit 5.

Visit 5 (at ~16 weeks): Each participant will undergo a history and physical examination and female participants will undergo a pregnancy test. All participants will then undergo fasting blood work followed by 2-hour oral glucose tolerance testing, questionnaires, testing on appetite, DXA scan, and energy intake measurement at a buffet meal at the NIH Clinical Center. They will meet with Nutrition Staff to review their 1-week food log and receive standardized education on a healthy diet and physical activity. Each participant will have the option to turn in stool samples collected at home or during their clinic visit. Used 1-month supply of liraglutide pens will be returned to research team. Liraglutide be will discontinued at this visit. The wrist accelerometer will be returned.

Visit 6 (off medication, at ~28 weeks): Each participant will undergo and history and physical examination. Weight, height, and waist circumference will be measured.

INTRODUCTION

1.4 STUDY RATIONALE

Obesity is a global epidemic that is associated with multiple co-morbidities and disability in both children [1] and adults. In the United States, in 2015-2016 [2], 20.6% of children and adolescents age 12-19 years had obesity (defined as BMI≥95th percentile for age and sex for the Centers for Disease Control standards [3]) and 7.7% had severe obesity (BMI ≥120% of the 95th percentile) [2]. Obesity-related diseases previously rare in adolescents [4-6] including type 2 diabetes [7-10], are increasingly diagnosed, with those having rapid early weight gain most at risk [11, 12]. The appearance of obesity-associated conditions in childhood leads to an earlier onset of related medical complications [13-15]; severe obesity also increases risk from COVID-19 infection [16-19]. Some [20-22] though not all [23-25] studies suggest pediatric obesity has a unique impact on later health, even independent of adult weight; Regardless, there is unanimity that adolescent obesity is a strong risk factor for persistence into adulthood and medical complications. Without effective strategies to treat adolescent obesity, millions of adolescents will enter adulthood with the physical and psychological consequences of excess adiposity. Adolescent obesity also has the potential to reverse the improvements in life-expectancy that occurred during the 20th century in the U.S [26, 27] and to cause more functional disability in those who survive to old age [28].

Initial management of obesity involves making lifestyle modifications to increase physical activity and adopt a healthy and well-balanced diet. However, most adolescents achieve only mild to moderate weight loss with reduction of BMI by -1 to -2 kg/m^2 and have difficulty implementing and sustaining their lifestyle changes [29]. Adolescents who continue to have severe obesity or have obesity with complications such as sleep apnea or diabetes despite lifestyle modification are sometimes prescribed pharmacologic agents, but options are limited; Orlistat, a lipase inhibitor is FDA approved for children ≥12 years, and phentermine, a norepinephrine reuptake inhibitor for short-term use (12 weeks) is FDA approved for adolescents >16 years [30, 31]. Both have modest efficacy with approximately 3% mean BMI reduction [30, 31]. Liraglutide, a glucagon-like peptide 1 (GLP1) agonist is the latest medication to be approved for chronic weight management in children 12 years and older with BMI ≥30 kg/m^2. A double-blind, placebo-controlled phase 3 study showed that after 56 weeks, patients treated with liraglutide achieved a statistically significant reduction in BMI SDS of -0.23 compared with no reduction in the placebo group (estimated treatment difference: -0.22; 95% CI, -0.37, -0.08; P =.0022) [32].

Other agents have also been used off-label in some pediatric patients with variable results and unknown long-term outcomes. Consequently, an increasing number of patients with moderate to severe obesity and its comorbidities who fail to lose weight despite lifestyle and pharmacologic intervention are undergoing metabolic and bariatric surgery (MBS), which is currently considered the most effective treatment of severe obesity and its associated comorbidities, and is recommended by both the American Society for Metabolic and Bariatric Surgery (ASMBS) and the American Academy of Pediatrics (AAP) [33, 34].

The two most common surgical approaches used in children and adolescents with obesity are sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). In 2015, 66.6% of cases were SG and 28.5% were RYGB among adolescents age 18-21 years who underwent MBS in the

United States[35]. SG involves removal of 80-90% of the greater curvature of the stomach and achieves weight loss by restricting food intake whereas RYGB entails creating a small gastric pouch from the upper stomach that is connected directly to the middle portion of the small intestine (jejunum), bypassing the rest of the stomach and the upper portion of the duodenum. RYGB induces both restriction and changes in absorption. Both SG and RYGB have also been proposed to alter the metabolic/humoral milieu to reduce drive to eat [36].

Weight loss occurs rapidly following RYGB and SG and generally reaches a peak by 12 months postoperatively. The Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, the largest prospective multi-center observational study to date in pediatrics with 242 adolescents (≤ 19 years of age, mean BMI of 53) showed that among 67 patients who had SG, BMI decreased from 50 kg/m^2 at baseline to 37 kg/m^2 (26% reduction) and among 161 patients who had RYGB, BMI decreased from 54 kg/m^2 at baseline to 39 kg/m^2 (28% reduction) three years post-operatively [37]. Thus, although most patients experienced significant weight loss with a 26 to 28% reduction in BMI following MBS, 75% still met criteria for obesity (BMI>30 kg/m^2; Figure 1). Furthermore, many patients experienced weight regain after reaching their weight nadir at approximately 1 year [37-41] that places them at continued risk for the metabolic consequences of obesity.

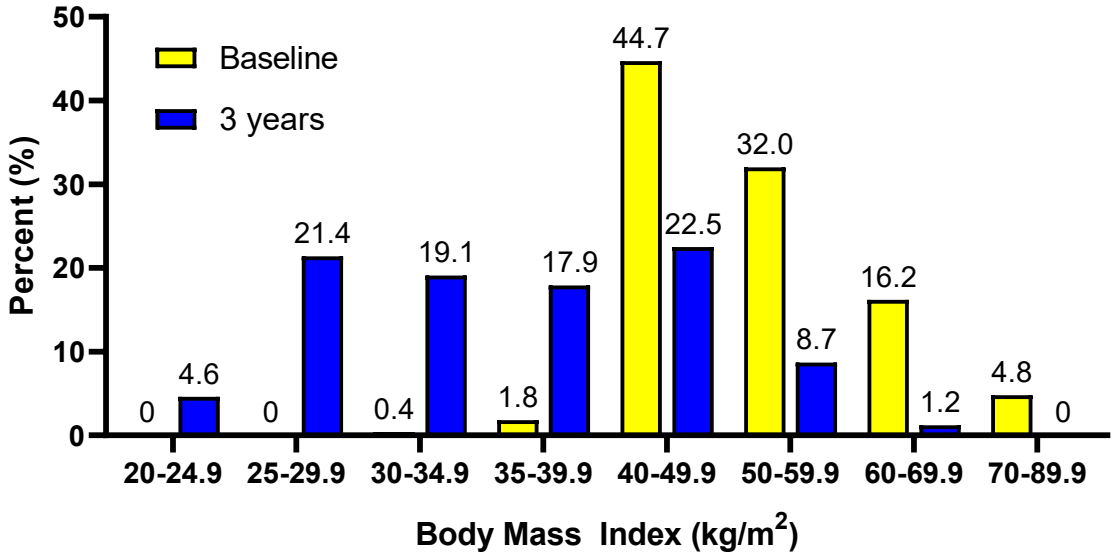


Figure 1: BMI at Baseline and Three Years After Adolescent Bariatric Surgery. Adapted from [37]. Only 26% achieved BMI <30 kg/m^2

To address how best to assist post-bariatric adolescents who continue to have obesity, we propose that the use of liraglutide, a glucagon-like peptide-1 (GLP1) agonist be studied in adolescent patients (age 12-20y) with BMI ≥30 or BMI ≥95th percentile for age and sex, 1 year or more after SG, which is now the most common pediatric bariatric operation in the United States. Results from this drug trial, if positive, may help develop a new pharmacologic option for refractory adolescent obesity and an opportunity to investigate the mechanism of action of

GLP-1 in treating children and adolescents with obesity post-bariatric surgery, a group uniquely resistant to treatment.

1.5 BACKGROUND

Liraglutide (Saxenda®) is an acylated human glucagon-like peptide-1 (GLP-1) agonist with 97% amino acid sequence homology to endogenous human GLP-1, an incretin hormone that activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylate cyclase by the stimulatory Gα-protein in pancreatic beta cells and other tissues [42]. Binding of liraglutide to pancreatic GLP-1 receptors increases intracellular cyclic AMP leading to protein kinase A (PKA) and guanine nucleotide exchange factor II (Epac2) activation. PKA and Epac2 alter ion channel activity; as a result, beta-cell ATP-sensitive potassium (KATP) channels are closed, which in turn shifts membrane potential and sensitizes beta cells to glucose [43]. Intracellular calcium (Ca2+) concentrations also rise through an elevated release from internal stores, resulting in an increase in the number of readily releasable insulin secretory vesicles; GLP-1 receptor activation also stimulates insulin gene transcription [44]. Thus, GLP-1 agonists lead to greater insulin release from beta cells, but only in the presence of elevated glucose concentrations. GLP-1 agonists also decrease glucagon secretion in the fasting state with subsequent decrease in hepatic gluconeogenesis [45], and act in the stomach to delay gastric emptying, though this latter effect is considered minor because of rapid tachyphylaxis [46]. Most interestingly, GLP-1 agonists reduce physiological hunger and long-term food intake via effects at multiple sites of action including peripheral ascending vagal fibers, neurons in the nucleus of the tractus solitarius, ventral tegmental area, the nucleus accumbens, and the hypothalamus [47]. These effects make GLP-1 agonists effective tools for the treatment of obesity.

Liraglutide is currently approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (dose 1.8 mg daily) and as a treatment of obesity in adults with a BMI ≥30 kg/m2 or BMI ≥27 kg/m2 with at least one weight-related comorbidity (dose 3 mg daily). The largest randomized, double-blind, placebo-controlled trial showed that among 3731 patients with overweight or obesity, the liraglutide group lost an average 8.4 kg of body weight vs. 2.8 kg with placebo at 56 weeks [48].

In children, liraglutide 1.8 mg/d dosing is FDA-approved to treat children 10 years and older with type 2 diabetes and the 3 mg/d dose was recently approved for chronic weight management in adolescents 12 years and older with body weight above 60 kg and an initial BMI ≥30 kg/m^2 as an adjunct to a reduced-calorie diet and increased physical activity. Recent data from a randomized, double-blind, placebo-controlled phase 3 trial of liraglutide for adolescents (n=251, age 12 to <18 years) with obesity (BMI ≥30 kg/m^2 and/or ≥95th percentile for age and sex) showed that use of liraglutide (3.0 mg) plus lifestyle therapy led to a significantly greater reduction in the BMI standard-deviation score (estimated difference -0.22; 95% confidence interval, -0.37 to -0.08; P=0.002) (**Figure 2**), BMI (estimated difference, -4.64 percentage points) and body weight (estimated difference, -4.50 kg [for absolute change]) than placebo plus lifestyle therapy [32]. Similarly, a randomized, double-blind, placebo-controlled trial including 24 children with mean age 9.9+/- 1.1 years and mean BMI Z-score of 3.9 showed that short-term treatment with liraglutide led to significant reduction in BMI Z-score from baseline to end of

treatment at 7-8 weeks (estimated treatment difference in BMI Z score -0.28; P=0.0062) with a comparable safety and tolerability profile to trials in adults with obesity with no new safety issues [49].

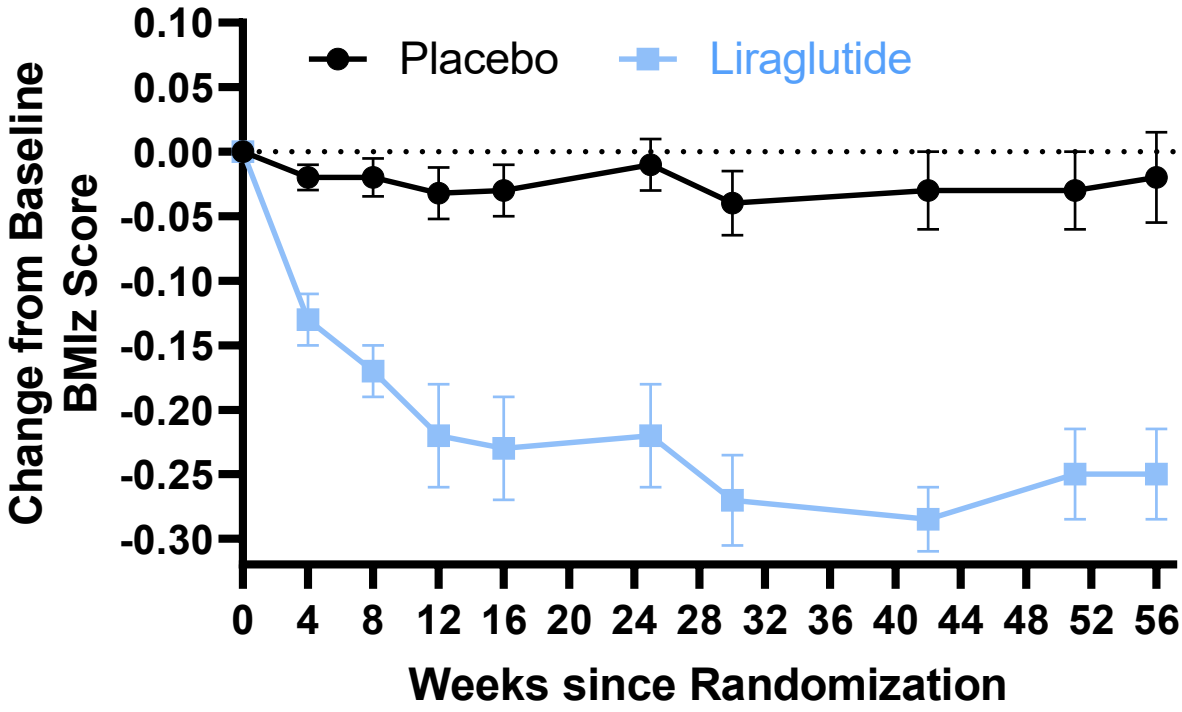


Figure 2: Absolute Change in BMI Standard-Deviation Score in adolescents with obesity who were randomized to liraglutide or placebo, Adapted from [32]

There are some relatively small, mostly retrospective studies on the use of anti-obesity pharmacotherapy in adult patients with weight regain or inadequate weight loss following MBS but none in children and adolescents. A retrospective review of 319 adults who had undergone RYGB (80.9%) or SG (19.1%) at two academic medical centers in the U.S. from 2000-2014 revealed that many patients who received weight loss medication after bariatric surgery had an additional weight loss benefit with mean added weight loss of -7.6% (17.8 lbs.) of total postsurgical weight [50]. Among the weight loss medications, topiramate was the most commonly prescribed (60.8% of patients) followed by phentermine (37.9%), metformin (38.6%), bupropion (23.%), and zonisamide (20.4%) [50]. Another retrospective study showed significant weight loss (-6.3 +/- 7.7 kg, P<0.05) among 117 adult patients treated with liraglutide 3.0 mg daily over 7.6+/- 7.1 months approximately 8 years post-bariatric surgery regardless of type of surgery (45% underwent RYGB , 43% underwent adjustable gastric banding, 12% underwent VSG) [51]. Liraglutide was also found to reduce body weight in adults (age 18 years and older) with expected weight loss but persistent or recurrent type 2 diabetes after metabolic surgery in the GRAVITAS study, a randomized, double-blind, placebo-controlled trial [52]. 80 adults who had undergone RYGB or SG at least 1 year before randomization were assigned to either liraglutide (1.8 mg daily) or placebo, and there was an estimated weight loss of -4.23 kg from

baseline to week 26 for liraglutide vs. placebo (95% CI 6.81 to -1.64, p=0.0017). In addition, 46% of patients in the liraglutide group lost 5% or more of their baseline bodyweight even on lower dose liraglutide (1.8 mg instead of 3 mg which is FDA approved dose for obesity treatment), compared with only 9% of patients in the placebo group. Thus, although there is retrospective data that suggests weight-loss medications may be beneficial following MBS, there are few published data from prospective trials which highlights the importance of research on this topic.

Among the available weight-loss medications, our team is most interested in investigating the use of liraglutide for post-bariatric patients because of known changes in GLP-1 and other incretin hormone levels like peptide-YY following MBS. Both RYGB and SG increase postprandial GLP1 and peptide-YY via rapid nutrient delivery down the GI tract where enteroendocrine L-cells are located [53], with some, though not all, studies finding lesser increases in GLP1 after SG than RYGB. Thus, we hypothesize that liraglutide treatment can augment the physiological increase in GLP1 following SG and cause weight loss via appetite suppression. Post-prandial GLP-1 responses appear to remain enhanced following SG up to 1 year following surgery, but it is unclear whether this effect persists beyond 1 year [54] and if it varies among patients with poor weight loss response (<20% BMI reduction) and those with typical weight loss (>20% BMI reduction) following MBS. Thus, it will be important to examine if extent of weight loss with liraglutide is impacted by amount of time (i.e. 1 year vs. multiple years) since surgery and by pre-treatment post-surgical weight.

1.6 Risk/Benefit Assessment

1.6.1 Known Potential Risks

1. Risks associated with liraglutide (Saxenda®):

Liraglutide for weight loss is approved by the FDA for use in adults with BMI ≥ 30 kg/m^2 or adults with BMI 27 kg/m^2 or greater in the presence of at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia) and in adolescents 12 years and older with body weight above 60 kg and an initial BMI ≥30 kg/m^2 as an adjunct to a reduced-calorie diet and increased physical activity. Novo Nordisk lists the following most common side effects of liraglutide on its package insert [57: nausea, diarrhea, vomiting, decreased appetite, indigestion, and constipation [42]. Possible serious side effects include: pancreatitis, hypoglycemia when used alone or with other blood glucose lowering medications such as insulin and sulfonylurea, kidney failure in patients who have kidney disease, serious allergic reaction, and acute gallbladder disease.

Recent data from a randomized, double-blind, placebo-controlled phase 3 trial of liraglutide (3.0 mg daily) for adolescents (age 12 to <18 years) with obesity (BMI ≥30 kg/m2 and ≥95th percentile for age and sex) showed that the percentage of patients who reported adverse events during the treatment period was similar in the liraglutide group (89%) and the placebo group (85%) [32]. However, more participants in the liraglutide group compared to placebo complained of gastrointestinal side effects, including nausea, vomiting, and diarrhea (64.8% vs. 36.5%) and had adverse events that led to discontinuation of trial treatment (10.4% vs. 0%).

Saxenda® comes with a black box warning for a risk of thyroid C-cell tumors as it causes thyroid C-cell tumors at clinically relevant exposures in both sexes of rats and mice. It is unknown whether Saxenda causes thyroid C-cell tumors, including medullary thyroid carcinoma in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined [42].

2. Blood sampling:

Peripheral blood draws (venipuncture) performed during this study for research will not exceed 5 ml/kg in a single day over any 8-week-trial period for pediatric patients (age less than 18 years) and will not exceed 10.5 ml/kg or 550 ml< whichever is smaller, over any 8-week-period. This amount falls below the NIH guideline for a safe amount of blood withdrawal. Possible side effects from blood draws include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection. We will offer ELA max cream to decrease pain. An area of white or red rash that usually goes away within a few hours may be seen after use of ELA max cream.

3. Radiation exposure from dual energy absorptiometry (DXA scan):

The DXA scan is a reliable and reproducible method to measure body composition, specifically body fat, bone mineral content, and lean body mass. The patient lies on a flat table with the x-ray source below the table and the detector above. For the iDXA scan used in this study, the total effective dose of radiation from the two scans performed is 0.00006 rem, which is below the guideline of 5 rem (for adults) and 0.5 rem (for children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If participants want to learn more about radiation, they will be given the pamphlet: An Introduction to Radiation for NIH Research Subjects. DXA is not painful but may be inconvenient because of the time needed to complete the study.

4. Oral Glucose Tolerance Test:

Dextrose solution administration is without known serious risks but may cause mild feelings of nausea or rarely lead to vomiting. Patients may develop transiently high blood sugar levels from the glucose, but it should normalize within a few hours and should not be clinically significant.

5. Other body composition methods

Body circumference measurements of the waist will be done with a flexible tape measure; this involves no risk and is not painful.

6. Accelerometer Testing:

Participants will be asked to wear an accelerometer on their wrist for 2 weeks at a time that measures free-living physical activity. It is an unobtrusive device without known risks and requires no maintenance by the user. It may cause mild inconvenience to the participant as they will be instructed to wear the accelerometer during all hours, except when bathing or showering

and for contact sports. If irritation at the site of the wrist strap occurs, the participant will be instructed to discontinue the use of the device and contact the research study team.

7. Questionnaires and interviews

Both questionnaires and interviews involve minimal risk. However, it is possible that participants may experience slight discomfort as a result of being asked to fill out questionnaires or respond to queries about stress and mood. If the wording of a question makes the participant uncomfortable, the participant is not required to answer that particular question. Similarly, participants will be informed of their right to not complete any test or task during any visit. Additionally, questionnaires and interviews may cause inconvenience because of the time required for testing.

8. Pregnancy/Birth control

The effects of liraglutide on the unborn child and on the newborn baby are not known. Because of this, it is important that participants do not participate if pregnant or breast-feeding. It is also important that participants do not become pregnant during the course of the study. Females with child-bearing potential will be required to undergo a pregnancy test prior to starting and throughout the study. Males will also be instructed not to father a child for at least 6 months after completion of the study. Those who are sexually active and not surgically sterile must use effective contraception.

9. The physical examination, body measurements with a tape measure, and vital signs are without significant risk, but some subjects may find them inconvenient for time required to complete. A limited physical examination will be performed in a concise but thorough manner with appropriate measures taken to provide participant's privacy.

10. Urine collections for pregnancy check are without significant risk, but some subjects may find them uncomfortable to collect.

11. Stool samples are also without significant risk, but some subjects may find them uncomfortable to collect. It is possible that we will send subject's stool to other scientists working with us on obesity-related studies, but in this case personal identifiers will be removed, and the samples coded or deidentified. If a subject chooses to withdraw from the study, we will keep samples for analysis indefinitely, unless the subject requests that the samples be destroyed.

12. The surveys and food records (diet log) are also without significant risk but may be inconvenient because of the time required to complete.

13. The buffet meal is without significant risk, but participants may feel uncomfortable if they eat too much or too quickly.

Alternatives to participation

Participation in clinical trials is completely voluntary. Refusal to participate will not affect a subject's ability to participate in other studies at NIH or elsewhere. The main alternatives to treatment include continuing or intensifying behavioral management strategies for obesity, or possibly using one of the FDA-approved treatments for obesity in adolescents: orlistat, a lipase inhibitor for children ≥12 years and phentermine, a norepinephrine reuptake inhibitor for short-term use (12 weeks) in adolescents ≥16 years or other medications such as phentermine plus topiramate that are approved for those age 17y and older. It is also possible a provider would prescribe liraglutide. None of these medications have been specifically approved by the FDA for use in adolescents who have undergone bariatric operations and thus would be considered being prescribed off-label.

1.6.2 Known Potential Benefits

This research protocol will investigate the use of liraglutide, a glucagon-like peptide-1 (GLP1) agonist in adolescent patients (age 12-20y) who continue to have obesity (BMI ≥30 kg/m^2 or ≥95th percentile for age and sex) 1 year or more after sleeve gastrectomy. Based on recent data from a randomized, double-blind, placebo-controlled phase 3 trial of liraglutide for adolescents (age 12 to <18 years) with obesity (BMI ≥30 kg/m2 and ≥95th percentile for age and sex), use of liraglutide (3.0 mg) plus lifestyle therapy is anticipated to have the potential to decrease the BMI of enrolled participants [32].

In addition, for enrolled patients with type 2 diabetes taking metformin, liraglutide is expected to improve glycemia based on results from the ELLIPSE trial, a 26-week, randomized, double-blind, parallel-group, placebo-controlled trial in 134 pediatric patients with T2D aged 10 years and older [55]. Patients were randomized to liraglutide or placebo once daily in combination with metformin, with or without basal insulin. At Week 26, treatment with liraglutide was superior in reducing A1C from baseline vs. placebo with an estimated treatment difference of -1.06% in A1c reduction from baseline (95% CI: -1.65, -0.46; p<0.001). In addition, the percentage of patients achieving an A1C <7% with liraglutide was 63.7% vs. 36.5% with placebo.

Participants will receive individualized counseling in nutrition from nutrition department staff at the NIH Clinical Center at their Screening Visit, but as such counseling is standard of care for patients with obesity, it is not considered a benefit of the study.

1.6.3 Assessment of Potential Risks and Benefits

This clinical drug trial and its associated testing will be associated with some risks which we will try to minimize as outlined below:

-To minimize the risk for gastrointestinal disturbance, liraglutide dosing will be gradually increased over a 5-week period to achieve a maximum dose of 3.0 mg daily. Participants who experience mild to moderate gastrointestinal symptoms will contact the study team and the dose of liraglutide will be decreased and maintained at maximum tolerated dose until completion of the study. Participants who experience severe and/or recurrent gastrointestinal symptoms including acute gallbladder disease will be withdrawn from the study.

-To minimize the risk for hypoglycemia for participants taking liraglutide, we will exclude patients on insulin or sulfonylurea therapy.

-To minimize the risk of pancreatitis in this study from liraglutide treatment, we will exclude patients with prior history of more than two episodes of pancreatitis as it may put them at higher risk for pancreatitis. If pancreatitis is clinically suspected (either based on signs/symptoms consisting of moderate to severe abdominal pain with nausea or vomiting) the following will take place: 1) Patient will be directed to local emergency department where amylase and lipase levels will be drawn 2) Abdominal ultrasound will be obtained. If a diagnosis of pancreatitis is likely or confirmed based on labs and/or imaging, the following additional actions will be taken. 1) The patient will be recommended for admission for further management or discharged home with supportive care depending on clinical severity. 2) Appropriate treatment will be initiated by primary medical team (usually, NPO and pain medications) if admitted. 3) The patient will be withdrawn from the study. 4) The IRB will be notified per guidelines for serious adverse effects.

-To minimize the risk of kidney failure in this study from liraglutide treatment, we will exclude patients with chronic kidney disease (eGFR <60; eGFR calculated using CKD-EPI equation).

-To minimize the risk of thyroid c-cell carcinoma from liraglutide treatment, we will exclude patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 (MEN-2) because use of Saxenda®is contraindicated in these patients. If a thyroid nodule or neck swelling is observed, further evaluation will be pursued with thyroid ultrasound and serum calcitonin measurement.

-To decrease pain from venipuncture, we will offer ELA max cream to participants.

-To decrease risk of infection from venipuncture, we will place intravenous catheter under sterile conditions and observe universal precautions.

OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
1. To determine the effect size for the change in BMI of liraglutide 3.0 mg subcutaneously at 16 weeks in adolescents who have obesity after SG	Estimation of required sample size for a later RCT through calculation of effect size for change in body mass index (BMI) from baseline to 16 weeks of liraglutide.	We will use the observed changes to determine the sample size of a subsequent randomized, controlled investigation.
Secondary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
1. To study the effects of 16 weeks of liraglutide 3.0 mg subcutaneously on change in BMI and fat mass in adolescents who underwent vertical sleeve gastrectomy (SG) ≥1y prior to study initiation but still have obesity or have a recrudescence of obesity after surgery. 2. To compare the effects of liraglutide on BMI and fat mass in enrolled participants who had a poor initial response to SG (<20% BMI reduction at BMI nadir) vs. those with a typical post-SG weight loss (≥20% BMI reduction at BMI nadir) 3. Tolerability and Safety of 3.0 mg liraglutide	Change from baseline to 16 weeks in: 1. BMI 2. Proportion reducing BMI by at least 5% and 10% 3. BMI standard deviation score for age and sex (BMIz) 4. Body weight Comparison of changes in BMI and fat mass after 16 weeks of liraglutide in participants who had a poor initial response to SG (<20% BMI reduction at BMI nadir) vs. those with a typical post-SG weight loss (≥20% BMI reduction at BMI nadir) Percentage of participants reaching the top liraglutide dose and all adverse events will be recorded.	BMI correlates with adiposity and obesity-related comorbidities such as hypertension, type 2 diabetes, sleep apnea, and dyslipidemia. Measuring the proportion of patients reducing their BMI by at least 5% and 10% will help better differentiate degree of weight loss with drug treatment. Percentage total body fat mass by DXA will be measured because weight loss with drug treatment may be associated with changes in body composition.
Tertiary/Exploratory		
1. To examine the effects of liraglutide in enrolled participants on changes in body composition, metabolic syndrome markers, energy intake, glucose tolerance, GI hormone concentrations, appetite, free living physical activity, mood,	1. Percentage total body fat mass by DXA 2. Appetite score using visual analog scale (VAS) 3. Attention bias to highly palatable images 4. Energy intake at buffet meal	Weight loss with drug treatment may affect obesity-related comorbidities/metabolic syndrome markers such as hypertension, dyslipidemia, glucose intolerance/diabetes. We will examine the effect of liraglutide on

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
suicidality, weight related quality of life, self-perception of body image, and secretome	5. Free living physical activity by accelerometry 6. Metabolic syndrome markers (waist circumference, systolic and diastolic blood pressure, lipids, fasting plasma glucose level) 7. Fasting plasma insulin level and HOMA-IR index 8. 2-hour oral glucose tolerance test (OGTT) insulin and glucose measurements 9. Hemoglobin A1C 10. Plasma GI hormones (GLP-1 and PYY) during OGTT 11. Weight related quality of life (QoL) score 12. Beck Depression Inventory total score 13. Body-Esteem Scale for Adolescents and Adults 14. Secretome analysis 15. Stool microbiome analysis 16. Columbia-Suicide Severity Rating Scale (C-SSR)	energy intake as it is known to suppress appetite. We will also examine effect of liraglutide on attention bias to highly palatable images as heightened attention bias to highly palatable images may lead to excess energy intake. Free-living physical activity with an accelerometer will be measured because weight change with drug treatment may affect energy expenditure. Weight related quality of life score, Beck Depression Inventory total score, Columbia-Suicide Severity Rating Scale, and self-perception of body image score will be measured to examine psychological effect of weight before and after drug treatment

STUDY DESIGN

1.7 OVERALL DESIGN

This trial will be a multi-site open-label Phase II non-randomized pilot study involving two US sites: NIH Clinical Center and CNH. Dr. Evan Nadler and Dr. Nazrat Mirza at CNH will be involved in identifying and recruiting potential participants. They will be involved in answering questions about the study from interested patients but will not be screening or obtaining consent from participants. They will also be analyzing identifiable information from participants. All study visits will be conducted at a single site (NIH Clinical Center) to investigate the efficacy of liraglutide, a glucagon-like peptide-1 (GLP1) analogue to promote weight loss in pediatric patients (age 12 to <21y) who continue to have obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile for age and sex) 1 year or more after vertical sleeve gastrectomy (SG) over 16 weeks.

Participants will undergo a telephone screening, followed by a screening visit to assess eligibility. Those found eligible will undergo a baseline evaluation to assess their glucose tolerance, lipids, levels of plasma GI hormones, appetite, body composition, energy intake, free living physical activity (by accelerometry), questionnaire measures, including assessment of weight related quality of life, mood, suicidality, and self-perception of body image. The trial will be divided into two consecutive periods. Period 1 will consist of 5 weeks of dose titration with goal of reaching max dose of 3 mg liraglutide daily with visits every 4 weeks over 16 weeks (including the 5 weeks of titration). The treatment period will then be followed by a 12-week period off study drug ending at week 28.

The primary outcome (change in BMI) will be statistically analyzed after participants have been treated with 3.0 mg daily liraglutide or max tolerated dose at 16 weeks. Secondary outcomes will also be measured at 16 weeks. BMI will be reassessed at follow-up at 28 weeks. There will be no interim analyses. Randomization will be stratified by birth sex assignment (Male versus Female), race (Non-Hispanic Black versus Other), and degree of weight loss after SG (those with typical post-SG weight loss, defined as ≥20% BMI reduction versus those with poor post-surgical weight loss response, defined as <20% BMI reduction post-SG), since expectation of benefit might differ in those unable to lose weight with SG.

1.8 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We propose a pilot open-label treatment study to estimate effect sizes and identify potential responders for a subsequent larger randomized, double-blind, placebo-controlled trial. Data will be compared for patients with poor weight loss response to SG (<20% BMI reduction) vs. those with typical post-SG weight loss (>20% BMI reduction) but who have persistent obesity (BMI ≥30 kg/m^2 or ≥95th percentile for age and sex) 1 year or more after SG. These data will allow determination of the sample size for a future fully powered randomized controlled trial.

1.9 JUSTIFICATION FOR DOSE

Eligible patients will be treated with daily subcutaneous liraglutide (starting at 0.6 mg daily with weekly dose escalations up to 3.0 mg per day or max tolerated dose). This dose is in line with liraglutide's treatment dose for adults with a BMI ≥30 kg/m2 or BMI ≥27 kg/m2 with at least one weight-related comorbidity (dose 3 mg daily).

In addition, a recent randomized, double-blind, placebo-controlled phase 3 trial of liraglutide for adolescents (age 12 to <18 years) with obesity (BMI ≥30 kg/m2 and ≥95th percentile for age and sex) used a treatment dose of 3.0 mg daily [32] and had a comparable safety and tolerability profile to trials in adults with obesity with no new safety issues [49].

STUDY POPULATION

Adolescents are selected as the study subjects because of the dearth of relevant data for adolescents who have undergone SG. All races and ethnicities will be included. Since obesity is identified in large percentages among minority groups including Asian Americans, African American and Hispanic Americans, we anticipate good representation of all major races/ethnicities. It is expected, given our recruitment procedures targeting individuals living in the greater metropolitan Washington, D.C. area, that we will recruit rates of minority participation in excess of their representation in the Washington, D.C. metropolitan area: 64.2% Caucasian, 27.2% African American and 8.6% Hispanic.

Total number of subjects to be studied in the protocol:	50 maximum
Planned number of subjects to be screened in person:	50 maximum
Planned number of subjects to be treated with liraglutide:	43 maximum

Subjects will not be replaced if they withdraw or become ineligible.

1.10 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, 12-20.999 years at screening visit
2. 12 months or more status-post vertical sleeve gastrectomy with a maximum of 10 years after surgery
3. BMI 30 kg/m^2 or ≥95th percentile for age and sex
4. In good general health as evidenced by medical history
5. Ability to take subcutaneous medication and be willing to adhere to the daily subcutaneous liraglutide regimen
6. Ability to provide consent/assent before any trial-related activities as required per protocol
7. Stated availability for the duration of the study

1.11 EXCLUSION CRITERIA

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

1. Current or recent (within 3 months of start of study drug initiation) use of weight loss medications such as phentermine, topiramate, lisdexamfetamine (prescribed specifically for weight loss; when prescribed for ADHD and dose is stable for last 3 months this medication will be allowed), orlistat, and naltrexone HCl/bupropion HCl, or liraglutide
2. Weight of more than 450 lbs. (because Dual-Energy X-ray Absorptiometry (DXA) scanning cannot be done in those exceeding this weight)
3. Current use of insulin or sulfonylurea or other medication affecting insulin secretion or GLP1 clearance such as a DPPIV inhibitor
4. Weight loss of more than 3% of body weight in the past 2 months
5. Current pregnancy, desire to become pregnant within study period, current lactation or, if sexually active, not willing to use adequate contraceptive measures
6. History of recurrent pancreatitis (greater than 2 episodes)
7. History of chronic kidney disease (eGFR <60)
8. History of gastroparesis
9. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
10. History of prior metabolic and bariatric surgery other than vertical sleeve gastrectomy
11. Current or prior use of any GLP-1 agonist medication during the 6 months before screening, including liraglutide.
12. Known or suspected allergy to trial medication, excipients, or related products
13. Treatment with another investigational drug or other experimental intervention within 3 months prior to enrollment in this trial
14. Individuals who have current substance abuse or a DSM 5 Axis I psychiatric disorder or DSM Axis II Mental Retardation diagnosis that in the opinion of the investigators would impede competence, compliance, or participation in the study
15. Suicidal ideation type 4 or 5, history of past suicide attempt, and suicidal behavior in the past month
16. Presence of a major medical illness not listed above

1.12 Inclusion of Vulnerable Participants

This study will involve recruitment of adolescents age 12-<21 years as the aim of the clinical trial is to determine the efficacy of liraglutide to promote weight loss in adolescent patients, a population with limited medical treatment options for moderate to severe obesity. The study will not involve recruitment of other vulnerable populations including pregnant women, prisoners, NIH employees, adults who lack consent capacity, including the mentally ill, and cognitively impaired participants because they do not meet the inclusion criteria for this study.

1.13 Inclusion of Pregnant Women, Fetuses or Neonates

Not Applicable

1.14 Lifestyle Considerations

Not Applicable

1.15 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently 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 use of weight loss medication like phentermine, topiramate, lisdexamfetamine, orlistat, and naltrexone HCl/bupropion HCl may be rescreened three months after discontinuing the medication. Rescreened participants should be assigned the same participant number as for the initial screening.

1.16 Strategies for Recruitment and Retention

Recruitment: A total of at most 50 participants to be screened at the NIH for protocol participation will be recruited from Washington, DC and local suburbs in Maryland and Virginia, with expected accrual rate of approximately 4 participants per month. Recruitment efforts will aim to enroll subjects in proportion to their representation in the population of Maryland. Subjects of all racial, ethnic and socio-economic backgrounds will be invited to participate in this study. Tools used for the recruitment of subjects will include the posting of the study description on the NIH Clinical Trials website. Additionally, flyers will be placed on bulletin boards at different buildings throughout the NIH campus and CNH. Recruitment material will be IRB approved prior to dissemination. Potential participants may also be referred by local providers responsible for clinical care. This includes providers from CNH's Bariatric Surgery Clinic and CNH's Obesity Program (multidisciplinary IDEAL Clinic) as well as from other community providers to whom we will provide our study information via a physician mailing letter and recruitment flyer. If necessary, further subjects will be recruited through newspaper advertisements or letter mailings. Advertisements will be submitted to the IRB before use.

Retention: There are incentives for attendance at study visits in terms of compensation for the time spent for, and inconvenience of, participation (see Compensation). We have a well-established track record of success in retaining participants with obesity for pharmacotherapy trials in adults and children [56-60]. For example, we recruited 340 adults for a 2-year pharmacotherapy RCT, retaining 82% for 1-year and 75% for 2-year study outcome measurements.

1.16.1 Costs

The trial drug will be provided at no cost to the patient. All trial related testing will be performed at no cost to the patient.

1.16.2 Compensation

Enrolled participants will be financially compensated for participation in this study for attending study visits as follows:

Compensation per visit- to be given at the end of each visit

1. Outpatient screening visit: $50
2. Baseline evaluation visit: $200
3. Interim Safety Visits (three total @$25 per visit): $75

4.	Visit 5	$200
5.	Optional stool samples (up to 2 @$25 per sample)	$50
6.	Final Visit:	$50
	Total=	$575 to $625

Compensation per procedure at Baseline evaluation visit:

1.	History and Physical Exam	$20.00
2.	OGTT	$50.00
3.	DXA	$30.00
4.	Accelerometer	$20.00
5.	Blood draw	$30.00
6.	Questionnaires	$50.00
7.	Optional Stool Collection	$25.00
	Total	$200 to $225.00

The participants will be compensated for the parts of the study that they have completed. Payments will be sent after the visit either by check or direct deposit. If the participant is a minor, the guardian will receive the visit payment on behalf of the minor subject.

Guardians accompanying minors to NIH will be compensated $40 per visit x 7 visits: $280 which will be paid as a lump sum at the completion of the study.

Travel expenses (mileage, Metro, or taxi fare) will also be reimbursed per NICHD guidelines.

STUDY INTERVENTION

1.17 STUDY INTERVENTIONS(S) ADMINISTRATION

1.17.1 Study Intervention Description

The following description is quoted from the FDA-approved package insert [61]: "SAXENDA contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is C172H265N43O51 and the molecular weight is 3751.2 Daltons."

"SAXENDA injection is a sterile, aqueous, clear, colorless or almost colorless solution for subcutaneous use. Each 1 mL of SAXENDA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. SAXENDA has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each prefilled pen contains a 3 mL solution of SAXENDA equivalent to 18 mg liraglutide (free-base, anhydrous)."

"Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). Like endogenous GLP-1, liraglutide binds to and activates the GLP-1 receptor, a cell-surface receptor coupled to adenylyl cyclase

activation through the stimulatory G-protein, Gs. Endogenous GLP-1 has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once-daily administration, is a result of self-association that delays absorption, plasma protein binding, and stability against metabolic degradation by DPP-4 and NEP."

Pharmacokinetics

"Absorption -Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 11 hours post dosing. The average liraglutide steady state concentration (AUCτ/24) reached approximately 116 ng/mL in obese (BMI 30-40 kg/m2) subjects following administration of SAXENDA. Liraglutide exposure increased proportionally in the dose range of 0.6 mg to 3 mg. The intra-subject coefficient of variation for liraglutide AUC was 11% following single dose administration. Liraglutide exposures were considered similar among three subcutaneous injection sites (upper arm, abdomen, and thigh). Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

"Distribution -The mean apparent volume of distribution after subcutaneous administration of liraglutide 3 mg is 20-25 L (for a person weighing approximately 100 kg). The mean volume of distribution after intravenous administration of liraglutide is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (greater than 98%).

"Metabolism -During the initial 24 hours following administration of a single [3H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

"Elimination -Following a [3H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 0.9-1.4 L/h with an elimination half-life of approximately 13 hours, making liraglutide suitable for once daily administration."

Liraglutide solution (6 mg/mL, 3 ml) for subcutaneous injection via a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2mg, 1.8 mg, 2.4 mg, and 3.0 mg will be used within the approved dosing regimens. Table 1 illustrates the titration schedule for the drug. The study intervention is commercially available and will be purchased. The intervention dose of 3.0 mg daily is approved by the FDA to treat children 12 years and older with body weight above 60 kg and an initial BMI ≥30 kg/m^2 (or above the International Obesity Task Force BMI Cut-offs for Obesity by Sex and Age for Pediatric Patients Aged 12 Years and Older) as an adjunct to a reduced-calorie diet and increased physical activity.

There will be no IND obtained for the use of any of the commercial agents used in this study. This study meets the criteria for exemption for an IND as this investigation is not intended to support a new indication for use or any other significant change to the labeling; the drugs are already approved and marketed and the investigation is not intended to support a significant

change in advertising; and the investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

We have received an IND exemption for the use of liraglutide (Saxenda®) in this study. The letter documenting this exemption has been supplied to the IRB.

1.17.2 Dosing and Administration

1.17.2.1 Dose Escalation

Table 1: Titration Schedule for Liraglutide

Study schedule	Week	Liraglutide (subcutaneous injection)
Screening	-1 to 0	-
Baseline visit	0-1	0.6 mg once daily as tolerated
	1-2	1.2 mg once daily as tolerated
	2-3	1.8 mg once daily as tolerated
	3-4	2.4 mg once daily as tolerated
Target study dose	4-16	3.0 mg once daily as tolerated

The participant will start the study drug at Visit 1 (Baseline Visit) after the History & Physical Examination. The study drug will be titrated to the highest tolerable dose as per Table 1 above.

1.17.2.2 Dose Limiting Toxicity

Adverse reactions occurring in ≥3% of SAXENDA-treated pediatric patients and more frequent than placebo are outlined in the Table below, from the package insert [61]:

	Placebo (N=126) %	SAXENDA (N=125) %
Nausea	14.3	42.4
Vomiting	4.0	34.4
Diarrhea	14.3	22.4
Hypoglycemia	4.0	15.2

Gastroenteritis	4.8	12.8
Dizziness	3.2	10.4
Pyrexia	7.1	8.0
Abdominal Discomfort	0.8	4.8
Constipation	2.4	4.8
Dyslipidemia	3.2	4.8
Fatigue	3.2	4.8
Cough	3.2	4.0
Depression	2.4	4.0
Dyspepsia	2.4	4.0
Pain in extremity	2.4	4.0
Injection site pain	3.2	3.2
Flatulence	0	3.2
Increased Blood Creatine Kinase	2.4	3.2
Increased Lipase	0.8	3.2
Rash	0	3.2

Participants on liraglutide may experience gastrointestinal side effects like nausea, diarrhea, vomiting, decreased appetite, indigestion, and constipation. Should a participant find these side effect intolerable, their dose will not be escalated (and may be decreased) according to tolerability as described below. In addition to tolerability, dose limiting toxicities are defined in the attached Excel file titled "CTCAE_v5.0_2017-11-27 for Liraglutide." In order to be dose limiting, the AE must be considered to be at least possibly due to the study drug.

1.17.2.3 Dose Modifications

If intolerable symptoms persist after 3 days at any dose, the liraglutide dosage will be decreased by 0.6 mg daily. If the highest tolerable liraglutide dose is less than 0.6 mg daily, the study drug will be discontinued, but the participant will be asked to return for Study Visit 5.

If gastrointestinal symptoms resolve, then at the discretion of the PI, the dose of liraglutide may be increased after 3 days to the previous dose. If participant redevelops GI symptoms on previous dose, then they should continue the max tolerated dose for the remainder of the study.

If a dose of liraglutide is missed, the study participants will be asked to resume the once daily regimen as prescribed with the next scheduled dose. They will be instructed not to administer an extra dose or increase the dose to make up for the missed dose.

1.17.2.4 Drug Administration

Prior to first use, Saxenda will be stored in a refrigerator between 36 to 46 degrees Fahrenheit as recommended on its package insert. Participants or their parent will administer first dose of study drug (0.6 mg) subcutaneously at Visit 1 after receiving training from our research team on proper injection technique. They will also be given a medication guide (see document titled, "Saxenda for patients." Subsequent subcutaneous doses will be administered at participants' home daily at a consistent time. After first use of the Saxenda pen, the pen will be stored at controlled room temperature (59 to 86 degrees Fahrenheit) or in a refrigerator (36 to 46 degrees Fahrenheit) with the pen cap on.

If a dose is missed, the participant should make up the missed dose on the same day as soon as they remember and take their next daily dose as usual on the following day. The participant should not take an extra dose of the drug or increase their dose on the following day to make up for the missed dose. Any missed doses will be recorded in a patient log.

Participants will call the research team if they miss their dose of study drug for 3 days or more.

The study drug dose will be up-titrated as show in Table 1.

1.18 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Liraglutide (Brand name Saxenda) will be purchased from Novo Nordisk and stored in the NIH Clinical Center Pharmacy in its original packaging for use as specified in the Package Insert. The NIH Clinical Center Pharmacy will dispense the study medication per study schedule. Study medication will be supplied in 30 days' supply at Visit 1-4.

1.18.1 Acquisition and Accountability

The study drug will be acquired and stored by the NIH Clinical Center Pharmacy. The investigator's team will pick up the study drug from the NIH CC Pharmacy at each study visit. There is no control product in this open label trial. Empty pens will be returned at Visits 2-5 and discharged by the investigator's team. The storage of medications will be according to the package insert for the study drug.

1.18.2 Formulation, Appearance, Packaging, and Labeling

Saxenda® solution (6 mg/mL, 3 ml) purchased from Novo Nordisk for subcutaneous injection via a pre-filled, multi-dose pen will be supplied. The solution is clear and colorless.

Participants will be requested to return all used pens as well as any expired or unused medication to Study Investigators, who will count used and unused pens and give them to the NIH pharmacy for disposal.

1.18.3 Product Storage and Stability

Prior to first use, Saxenda® should be stored in a refrigerator between 36 degrees Fahrenheit to 46 degrees Fahrenheit. After initial use of the Saxenda® pen, the pen can be stored for 30 days at controlled room temperature (59F to 86F) or in a refrigerator (36F to 46F). The pen cap

should be kept on when not in use. Saxenda® should be protected from excessive heat and sunlight. The needle should be always removed and safely discarded after each injection [42].

1.18.4 Preparation

No preparation by study staff and/or study participants is required.

1.19 Measures to Minimize Bias: Randomization and Blinding

Not applicable as this is an open-label pilot study.

1.20 Study Intervention Compliance

Administration of study intervention will be observed at Visit 1. Subsequent administration of study intervention will be verified by inspecting drug supply at Visits 2-5. One-month supply of medication will be dispensed by the NIH pharmacy at Visits 1-4. At each visit, participants will be instructed to return all used and unused study medication. The study team will count/record the number of unused pens as a measure of medication adherence.

1.21 Concomitant Therapy

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.

Participants will be allowed to continue home medications (prescription medications, over-the-counter medications, and supplements) as long as they are not insulin, sulfonylurea, DPPIV-inhibitor or weight loss medications such as phentermine, topiramate, lisdexamfetamine, orlistat, and naltrexone HCl/bupropion HCl. All home medications and supplements will be recorded at screening and each study visit.

Liraglutide slows gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. Thus, caution should be exercised when oral medications are concomitantly administered with liraglutide [42] and participants will be recommended to take their oral medications separate from liraglutide if possible.

STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

1.22 Discontinuation of Study Intervention

Discontinuation from liraglutide 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 after enrollment (including, but not limited to changes from baseline), 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:

-History and physical

-Bloodwork per investigator discretion

-The specific underlying reason for discontinuation of study intervention or participant discontinuation/withdrawal

Participants are free to withdraw from participation in the study intervention at any time upon request. Study medication can be discontinued abruptly without untoward effects from medication withdrawal.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Completion of study intervention
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Investigator discretion
- Positive pregnancy test or intention of becoming pregnant
- Participant unable to receive Liraglutide for 1 week or more
- Initiation of obesity or diabetes medications or obesity treatments not permitted during the trial

1.23 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Prior to removal from study for adverse events, efforts will be made to have all subjects complete a safety visit approximately 14 days following the last dose of study therapy and to have them return at the scheduled time for Study Visit 5.

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

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Subject has completed the study follow-up period
- Death
- Screen Failure

The reason for participant discontinuation or withdrawal from the study will be recorded on the Withdrawal Case Report Form (CRF). Subjects will be excluded if they have any verified abnormality in laboratory values or physical status that cannot be explained by a mild intercurrent illness (or by obesity and insulin resistance itself) that in general are considered

CTCAE 5 grade 3 or greater [62]. Problem-specific stopping rules by CTCAE5 category will be prepared in conjunction with this protocol.

Subjects who sign the informed consent form and are scheduled to be treated but do not receive the study intervention may be replaced. Subjects who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

Investigator error leading to initiation of treatment in an ineligible subject will lead to treatment discontinuation as soon as the error is uncovered. Should discontinuation be required for any reason, no tapering of liraglutide is necessary; subjects will be requested to return all unused medication.

1.24 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for three scheduled visits and is unable to be contacted by the study site staff.

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 and reschedule the missed visit within 1-4 days 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 or 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

STUDY ASSESSMENTS AND PROCEDURES

The specific timing of procedures/evaluations to be done at each study visit are captured in Section 1.4, Schedule of Activities (SOA).

1.25 SCREENING PROCEDURES

Potential participants will be mainly referred by providers at CNH who are coinvestigators for this study. Dr. Evan Nadler , our research collaborator, is a pediatric surgeon at CNH who performs 75-125 cases of laparoscopic sleeve gastrectomy each fiscal year, which should provide ample participants. In addition to providers from the CNH Bariatric Surgery Clinic and CNH Obesity Clinic, referrals will also be accepted from other community providers to whom we will provide information about our study (see recruitment strategies). Interested participants will be given our study information and will contact us via the study line or email. Participants will be phone screened to determine baseline eligibility and additional study information. If participants are eligible, we will arrange a screening/enrollment visit at the NIH.

If potential participant is a patient at CNH, we will request permission to review medical records from Children's National Hospital by having families fill out a medical records request form.

Subjects who appear eligible when evaluated during a phone screening intended to assess general health and body weight/height (to determine BMI) will attend a screening visit at the NIH Clinical Center, during which their eligibility will be determined. History and physical examination will be conducted by a licensed practitioner. Pregnancy testing will be reviewed before subjects proceed with protocol related testing and treatment.

1.25.1 Screening activities performed prior to obtaining informed consent

Initial recruitment and eligibility screening will occur by telephone in response to a message from a participant interested in joining the study. Screening will occur on a continuous basis until recruitment is complete. Eligible subjects will then be scheduled for an outpatient visit. Eligible subjects will be mailed or emailed paperwork in advance, including the NIH medical history form, as well as the study consent form (s).

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects. Each subject will receive a written explanation of the purposes, procedures, and potential hazards of the study (refer to attached consent form). The scripts used at telephone screening are submitted for IRB review.
- Review of existing medical records to include H&P, vital signs measurements, laboratory studies, etc.

1.25.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for this study. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

All screening tests and procedures must be performed within 28 days prior to enrollment.

1. **Protocol review and signing of consent/assent forms**.
2. **Complete medical history and physical exam** with weight (in kg) measured while the subject wears light clothes, height (in cm) measured in triplicate, and body temperature, heart and respiratory rate, and a blood pressure measurement. Subjects will rest for 5 minutes in the seated position with the cubital fossa supported at heart level when blood pressure measurements are made. A detailed history will be taken. If a potential subject is noted to meet any of the exclusion criteria, that individual will be dismissed without further evaluation and referred for any required treatment to their usual physician.
3. **Fasting blood** for complete blood count, HbA1C, electrolytes, glucose, renal, mineral, lipid and hepatic profiles, ESR, CRP, 25-OH vitamin D level, urine or serum beta HCG (female participants only), and PT/PTT.

Subjects will be counseled that once results of the screening visit are known, they will be contacted with information on their eligibility to participate in the full study.

Information regarding the key assays used for eligibility criteria and other metabolic syndrome components (all measured by the NIH Clinical Center Laboratory Medicine Department):

a. Glucose:

@75mg/dL	: intraassay CV 2%	interassay CV 3%
@ 379 mg/dL	: intraassay CV 1%	interassay CV 2%

Sensitivity: 1 mg/dL

b. Insulin:

@ 24.2 µU/mL	: intraassay CV 1.2%	interassay CV 6.0%
@ 82 µU/mL	: intraassay CV 1.0%	interassay CV 2.5%

Sensitivity: 0.2uU/mL

c. Triglycerides:

@ 68 mg/dL	: intraassay CV 3%	interassay CV 4%
@384 mg/dL	: intraassay CV 2%	interassay CV 2%

Sensitivity: 2 mg/dL

d. HDL cholesterol:

@ 26 mg/dL	: intraassay CV 2.3%	interassay CV 2.7%
@ 47 mg/dL	: intraassay CV 1.6%	interassay CV 2.3%
@ 67 mg /dL	: intraassay CV 1.9%	interassay CV 2.1%

Sensitivity: 3 mg/dL

e. Hemoglobin A1c:

@ 5.1%	: intraassay CV 0.4%	interassay 1.11%
@9.9%	: intraassay CV 0.5%	interassay 0.73%

Sensitivity: 4.2%

1.26 EFFICACY ASSESSMENTS

1.26.1 Clinical Evaluations

Physical examination: Participant's height (on a calibrated stadiometer), weight (on a calibrated scale), waist circumference (using a non-stretching tape measure), and vital signs (temperature, pulse, respirations, blood pressure) will be measured. A complete physical examination (including review of peripheral lymph nodes, head, eyes, ears, nose, mouth and oropharynx, neck, heart, lungs, abdomen, musculoskeletal, extremities, neurologic, skin, and Tanner staging) will be performed at Visit 1 and 6. At other visits, a symptom-directed history and physical examination will be done. At all visits, participant's height (in cm), weight (in kg), and vital

signs will be measured. Body mass index (BMI, kg/m^2) will be calculated and used to determine BMI-SDS according to the Centers for Disease Control standards for age and sex [3]). Subjects will rest for 5 minutes in the seated position with the antecubital fossa supported at heart level when blood pressure measurements are made.

Imaging assessment: The participant will undergo a DXA scan at Visit 1 and 5. The participant will lie on a flat table with the x-ray source below the table and the detector above. Participants will undergo DXA scans in the Metabolic Clinical Research Unit (MCRU) using the Lunar iDXA (GE Healthcare, Madison, WI, USA) machine. The scan takes approximately 5-10 minutes. An external standard, simulating bone, fat, and muscle, is scanned once a week to validate measurements. This standard allows calculation of total body fat, muscle, and bone mass, and percentage of body fat. For the iDXA scan used in this study, the total effective dose of radiation from the two scans performed is 0.00006 rem, which is below the guideline of 5 rem (for adults) and 0.5 rem (for children) per year allowed for research subjects by the NIH Radiation Safety Committee.

Energy intake at buffet meal: Participants will be introduced to a buffet test meal (>10,000 kcal), varied in macronutrients (54% carbohydrate, 12% protein, 33% fat) and comprised of foods that most children like [63] (**Appendix 12**). Should any participant adhere to a specific dietary regimen for religious, ethical reasons or other reasons, if possible, the foods on the buffet may be substituted to meet such requirements. The participant will receive a tape-recorded instruction to "Let yourself go and eat as much as you want." Duration of eating is measured from the time the experimenter leaves the room until the participant indicates eating is completed. All foods are weighed on electronic balance scales in gram weights to the nearest gram; foods consumed are determined by subtracting the food weights after the participant's meal from initial weights. Food energy and macronutrient content are calculated using the USDA National Nutrient Database for Standard Reference. The energy and macronutrient content of the consumed meal is calculated by the ProNutra (Viocare Technologies) program. Nutrition staff preparing and measuring food for the buffet have yearly HACCP food safety training that focuses upon safe food handling, proper temperatures, hand washing, and using gloves for handling foods. All nutritionists also have had training in weighing/processing foods for controlled feeding studies to ensure consistency in the method and presentation. Participants will complete a brief series of visual analog scales and rating forms to assess appetitive states (e.g., hunger, satiety, fullness, nausea, drowsiness, calmness, desire to eat) prior to and after the test meal, [64-67]. Participants will also complete the following state mood questionnaires immediately before and after the test meal (unless otherwise noted) (**Appendix 11**):

1. *Brunel Mood Scale (BRUMS)* [68] is reliable and well-validated [68, 69]. The respondent rates his/her mood "right now" on a 5-point Likert scale based on 24 mood descriptors.
2. *Positive and Negative Affect Schedule, Expanded Version (PANAS-X)*: The PANAS-X captures both negative and positive mood states; for the current study, we will only assess guilt using the six-item subscale PANAS-X [70].
3. *State-Trait Anxiety Inventory (STAIC) – State Form* [71] will be used to measure pre-post meal state anxiety.

4. *LOC Severity* will **only** be assessed immediately following the test meal. Comparable to the EMA protocol described above, items adapted from the EDE will assess the degree to which LOC was experienced during the test meal.

Attention bias to highly palatable images: The *Palatable Food Cue Attention Bias Task (PFCBT)* will examine neural responses during a palatable food cue visual-probe paradigm with high and low palatability foods and neutral non-food household items. The same images and task protocol were used in our pilot study of food cue attention biases [72]. Similar palatable food images have been used effectively in neuroimaging studies of adults with binge eating disorder [73, 74] and non-treatment adolescents [75]. Visual-probe paradigms assess attention biases by presenting stimulus pairs followed by a probe that requires a response. Each trial will consist of a fixation probe in the center of the screen followed by an image pair presentation. Pairs of each picture combination (e.g., high palatability food-neutral, low palatability food-neutral, high-low palatability food, neutral-neutral) will be presented in randomized order. After the image pair disappears, a probe appears in one of the previously occupied photo locations. Youth respond with a right or left sided keypress to indicate the orientation of the probe. Youth will be instructed to respond as quickly and accurately as possible to the probe. Trials consist of a mixture of incongruent trials (when the probe replaces the neutral non-food household items), congruent trials (when the probe replaces the food images), and neutral trials (when two identical neutral non-food household items appear and the probe location is insignificant). The spatial location of images and probes are counter balanced.

Free living physical activity and sleep by accelerometry: Participants will be asked to wear an accelerometer on their body that measures free-living physical activity. The participant will be instructed to wear the accelerometer during all hours, except when bathing or showering for 2 weeks and to return the accelerometer in person or via mail after completion. We will use the ActiGraph GT3X+ activity monitor (ActiGraph, Pensacola, FL), which is worn like a wristwatch and delivers 24-hour physical activity and sleep/wake measurements. We have used this device successfully in other protocols with adolescents (15-CH-0096) [76, 77]. Outcomes include raw acceleration, activity counts, energy expenditure, physical activity intensity, body position, and sleep duration. A triaxial accelerometer and integrated ambient light sensor assist with enhancing the validity of data collected regarding sleep/wake times. The GT3X+ can store over 40 days of raw data, and its rechargeable battery is capable of providing power for 30 days between charges. Data will be downloaded and reduced using Actilife software (ActiGraph). In young adults, the GT3X+ is a valid and reliable device for detecting sleep/wake diurnal patterns, and has demonstrated good concordance with polysomnography [78]. The GT3X+ wrist actigraphy has also been used to assess sleep behavior in adolescents [79, 80].

Patient questionnaires:

Quality of life assessments-

Impact of Weight on Quality of Life-Lite (IWQOL-Lite)[81]

The IWQOL-Lite is a validated 31 item self-report measure of obesity-specific quality of life questionnaire. The IWQOL-Lite provides a total score inclusive of 5 domains: physical function, self-esteem, sex life, public distress, and work. The questionnaire is responsive to weight loss and gain, sensitive to treatment seeking status as well as to the degree of obesity. The IWQOL-Lite will be conducted in participants ≥18 years of age according to the SOA.

The Impact of Weight on Quality of Life (IWQOL)-Kids version for adolescents [82] will be used in all patients in this study.

SF-10 Health Questionnaire for Children

The SF-10 Health Survey for Children is a parent-completed survey that contains 10 questions adapted from the Child Health Questionnaire. The SF-10 provide coverage across a wide range of domains and is scored to produce physical and psychosocial health summary measures. The SF-10 will be conducted in participants <18 years of age according to the SOA.

Mental Health Assessments-

Beck Depression Inventory (BDI-II)-

The Beck Depression Inventory (BDI) is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression [83]. BDI-II was revised in 1996 to be more consistent with DSMIV criteria for depression in adolescents and adults (age 13-80) [84].

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool used not only to predict suicide attempts but to assess the full range of evidence-based ideation and behavior items, with criteria for next steps (e.g., referral to a mental health professional [MPH]). There are 2 versions of the C-SSRS that will be administered according to the SOA:

1) **The Baseline/Screening** version of the scale combines the Baseline and Screening forms to assess suicidality in a patient's lifetime and during a predefined time. This version can assess a patient's lifetime suicidality for data collection purposes as well as eligibility based on inclusion/exclusion criteria.
2) The **Since Last Visit** version of the scale assesses suicidality since the patient's last visit. This version is meant to assess participants who have completed at least one initial C-SSRS assessment and will be used in every subsequent visit. The 'Since Last Visit' version of the C-SSRS is asking about any suicidal thoughts or behaviors the patient/participant may have had since the last time the C-SSRS was administered.

To be eligible for the study, a patient cannot have a suicidal ideation of type 4 or 5, any lifetime history of a suicide attempt, or any suicidal behavior in the last month.

Hollingshead Two Factor Index of Socioeconomic Status [85] will be obtained for the parents/guardians of the participant.

Body-Esteem Scale for Adolescents and Adults

The Body-Esteem Scale for Adolescents and Adults is a 23-item measure with subscales of general feelings regarding own's own appearance, one's perception of others' evaluation about one's body and appearance, and weight satisfaction [86]. Reponses regarding agreement with item statements are provided on a 5-point Likert scale ranging from never (1) to always (5) with higher scores indicating more positive body-esteem.

Diet and Nutritional Counseling

Nutritional counseling and monitoring will be performed by nutrition department staff. Nutrition department staff will review food log with participants.

Order of Assessments

When scheduled at the same time point, the order of procedures should be as follows: obtain vital signs, perform history and physical examination, perform blood testing (at the specified time point, if applicable), perform DXA scan, perform computerized visual probe task of sustained attention, have participant answer questionnaires, and eat buffet meal (measure appetite score before and after). Adjustments may be made depending upon specific circumstance.

1.26.2 Biospecimen Evaluations

Blood Sample Collection: As indicated below, the amount of blood that will be obtained from adult participants (i.e., those persons 18 years of age or older) for research purposes will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period. For pediatric patients, no more than 5 mL/kg will be drawn for research purposes in a single day, and no more than 9.5 mL/kg will be drawn over any eight-week period. Approximately 11 mL will be collected at screening (CBC, acute care, mineral, hepatic, Vitamin D, CRP, ESR, A1c).

Oral glucose tolerance test (OGTT): Participants will undergo a 75 gram oral glucose tolerance test with blood samples collection at 0, 15, 30, 60, 90 and 120 minutes for hormones and metabolites (including glucose, insulin, glucagon-like-1 peptide, and peptide YY). It is certain that all participants will exceed 43 kg, and thus all will receive the adult dose (75 g) rather than require any calculation to determine dose. The homeostatic model assessment of insulin resistance (**HOMA-IR**) will be calculated from fasting ($_f$) insulin (I) and glucose (G): G_f (in mg/dL) x I_f in (μIU/mL/ 405). The **Matsuda index** (10^4/([G_f x 18] x I_f x [mean G_{OGTT}x18] x mean I_{OGTT})$^{0.5}$) will be calculated from the OGTT values. The diagnosis of impaired fasting glucose, impaired glucose tolerance, and diabetes will be made according to standard criteria.

Laboratory evaluations: The following tests will be drawn in fasting state: plasma glucose, lipids, glycosylated hemoglobin A1c. The lipid profile will include total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides. Samples to save for future research will also be obtained (~20 mL).

1.26.3 Correlative Studies for Research/Pharmacokinetic Studies

Blood samples will be collected for secretome analysis by SomaScan [87] (10 mL at baseline and follow-up) and for future research (20 mL). For SomaScan, obtained serum will be immediately stored at –80°C until further analysis without being exposed to freeze-thaw cycles. Serum proteomic analysis will use the SOMAscan 1.3k Assay (SomaLogic, Boulder, CO). This aptamer-based assay can detect 1305 protein analytes in human serum.[88] The proteins quantified include cytokines, hormones, growth factors, receptors, kinases, proteases, protease inhibitors, and structural proteins. A complete list of analytes measured can be found at http://somalogic.com/wp-content/uploads/2017/06/SSM-045-Rev-2-SOMAscan-Assay-1.3k-Content.pdf. Concentrations are measured as Relative Fluorescence Units. The assay will be performed according to manufacturer specifications, with data inspection using a web tool, as previously described.[89].

1.26.4 Samples for Genetic/Genomic Analysis

1.26.4.1 Description of the scope of genetic/genomic analysis

- None.

1.26.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

- Not Applicable

1.26.4.3 Management of Results

- Not Applicable

1.26.4.4 Genetic counseling

- Not Applicable

1.27 SAFETY AND OTHER ASSESSMENTS

Adverse events will be monitored via telephone and at all clinic visits using structured case report forms. If any participant develops any concerning adverse events reported by telephone, the individual will be scheduled for an immediate clinic appointment with a trial investigator for further work up, as necessary. Adverse events will also be assessed during the trial via vital signs (blood pressure, heart rate, temperature, respiratory rate), interim history, and the symptom-directed physical examination, as well as by laboratory studies of electrolytes, hepatic, metabolic, and systemic function. There are no EKGs or radiographic assessments for safety.

Physical examination:

Participant's height and weight will be measured; a targeted physical examination (including cardiac, respiratory, gastrointestinal, and neurological assessment) will be performed as part of safety assessment.

Vital signs:

Temperature, pulse, respirations, and blood pressure will be measured as part of safety assessment.

Questionnaires:

Beck depression survey, C-SSR, and Body Esteem Survey will be scored by research team members. The Beck depression survey and C-SSR will be scored on the same day the participant completes the questionnaires. All scores that raise concerns of current suicidality or current major depression will be reported on same day of completion/scoring to Dr. Zenno, NP Sheila Brady, or Dr. Yanovski who will determine need for follow-up.

Hollingshead Two Factor Index of Socioeconomic Status [85] will be obtained from the participant or parents/guardians of the participant only at baseline.

Injection Site Evaluation and Scoring

Injection sites will be carefully inspected, evaluated, and scored during the study period. The injection site evaluation will include identification and measurement of areas of erythema,

edema, and induration, as well as the presence of localized pain, tenderness, and itching. A sample injection site evaluation form is included in the Appendix.

In addition, unscheduled evaluations may also be recorded as warranted by clinical conditions, including in the interval between scheduled visits.

Biological specimen collection and laboratory evaluations:

Safety laboratory tests will include: CBC with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO2, albumin, total protein, glucose, BUN, creatinine, uric acid, AST, ALT, GGT, CPK, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, calcium, phosphorus).

a. Screening Visit	All Participants
i. Acute care, mineral, hepatic, 25-OH vitamin D, CRP	3.5 mL
ii. CBC, HbA1c	3.3 x 2 = 6.6 mL
iii. ESR	1.1 mL
iv. PT/PTT	1 mL
Total	12.2 mL
b. Visit 1	All Participants
i. Acute care, mineral, hepatic, lipid panel, 25-OH vitamin D, Insulin level, CRP	3.5 mL
ii. CBC, HbA1c	3.3 x 2 = 6.6 mL
iii. ESR	1.1 mL
iv. 2-hour OGTT	6 mL
v. Plasma GI hormones (GLP-1 and PYY)	3 mL
vi. Research Plasma and serum	16 ml
Total	36.2 mL
c. **Visit 5 (16 weeks)**	All participants
i. Acute care, mineral, hepatic, lipid panel, 25-OH vitamin D, Insulin level, CRP	3.5 mL

ii.	CBC, HbA1c	3.3 x 2 = 6.6 mL
iii.	ESR	1.1 mL
iv.	2-hour OGTT	8 mL
v.	Plasma GI hormones (GLP-1 and PYY)	3 mL
vi.	Research Plasma and serum	16 ml
	Total	38.2 mL

Results of clinical laboratory testing will be provided to participants on request.

1.28 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

1.28.1 Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

1.28.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

1.28.3 Classification of an Adverse Event

1.28.3.1 Severity of Event

All AEs will be assessed by the study clinician using the NCI Common Terminology Criteria for Adverse Events (CTCAE) 5.0 as the protocol defined grading system.

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

- **Mild** – asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Such events do not interfere with the participant's daily activities.

- **Moderate** – local or non-invasive intervention indicated; limiting age-appropriate ADL Such events result in a low level of inconvenience or concern with the therapeutic measures.
- **Severe** – medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limiting self care ADL Events that interrupt a participant's usual daily activity 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".
-

1.28.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator 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. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **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, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). 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.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **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.]

1.28.3.3 Expectedness

Expected adverse reactions are AEs that are known to occur for the study intervention being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. The source of the reference safety information used to determine the expectedness of the AE will be the package insert (approved labeling) for liraglutide approved for adults. Expectedness is assessed based on the awareness of AEs previously observed, not on the basis of what might be anticipated from the properties of the study intervention.

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. These determinations will also be reviewed by the study Safety Officer.

Liraglutide administration has known adverse consequences, delineated in the SAXENDA package insert [61]. If the rate or severity of these such consequences exceeds the rate or severity anticipated in the FDA-approved package insert, the events will be classified and reported as Unanticipated Problems, but otherwise will be considered expected events that will be described and reported to the IRB and DSMB at each Continuing Review.

We also anticipate that other mild symptoms may occur in the course of participation in the protocol unrelated to study drug or participation, with mild signs/symptoms (CTCAE Grade ≤ 2), such as rhinorrhea, nasal congestion, watery eyes, cough, lightheadedness, mild wheezing, menstrual cramps, muscle weakness, fever blister, mild urinary tract infection, etc., that occur infrequently (≤ 20%). These will also be summarized and reported to the IRB and DSMB at the time of Continuing Reviews.

1.28.4 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.

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 study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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 principal investigator or associate investigators will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after 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.

1.28.5 Adverse Event Reporting

Events occurring during this study will be reported to the NIH IRB per policy 801.

The Safety Officer monitoring this trial and the NICHD Clinical Director will also be sent reports of all Reportable Events following the same timelines as required for IRB reporting.

We anticipate that mild symptoms may occur in the course of participation in the protocol unrelated to study drug or participation, with mild signs/symptoms (CTCAE Grade ≤ 2), such as rhinorrhea, nasal congestion, watery eyes, cough, lightheadedness, mild wheezing, menstrual cramps, muscle weakness, fever blister, mild urinary tract infection, etc., that occur infrequently (≤ 20%). These will be summarized and reported at Continuing Review.

1.28.6 Serious Adverse Event Reporting

Events occurring during this study will be reported to the NIH IRB per policy 801.

Each patient must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (e.g., “How are you feeling?”) and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from participants.

All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

The study Principal Investigator will report to the NICHD Clinical Director any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event within 24 hours from the point in time when the Investigator becomes aware of the SAE. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis).

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the NICHD Clinical Director and should be provided as soon as possible.

The study Principal Investigator will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the PI's initial receipt of the information. In addition, the PI must notify FDA and all participating investigators in a safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the PI determines that the information qualifies for reporting.

All serious adverse events will be reported by the PI verbally and in writing as soon as possible to the NICHD Clinical Director. All adverse events (serious and non-serious, expected and unexpected) will be reported annually to the IRB and NICHD Clinical Director for review. Electronic data sheets or summary language will be supplied for IRB review of adverse event reports at continuing reviews.

The PI (***Jack A. Yanovski, MD, PhD***) will report adverse events in iRIS, to the IRB and to the NICHD Clinical Director in writing.

1.28.7 Events of Special Interest

None expected.

1.28.8 Reporting of Pregnancy

The effects of liraglutide on the unborn child and on the newborn baby are not known. Thus, it is important that participants do not become pregnant during the course of the study. Females with child-bearing potential will be required to undergo a pregnancy test prior to starting the study. Pregnancy testing will be monitored during the study. Males will also be instructed not to father a child for at least 6 months after completion of the study. Those who are sexually active and not surgically sterile must use effective contraception. If a female participant were to become pregnant during the study, she would be instructed to discontinue the study intervention and would end study-related visits. We would however contact the participant to ascertain the outcome of the pregnancy. If a male participant were to father a child during the study, the mother of his child would be recommended to have close clinical obstetric follow-up.

1.29 UNANTICIPATED PROBLEMS

1.29.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a

greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

1.29.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801.

1.29.3 NIH Intramural IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NIH Intramural IRB.

STATISTICAL CONSIDERATIONS

1.30 STATISTICAL HYPOTHESIS

- Primary Endpoint:

  The Primary Endpoint is estimation of required sample size for a later RCT through calculation of effect size for change in body mass index (BMI) from baseline to 16 weeks of liraglutide. The hypothesis is: The data will be sufficient to calculate the effect size for change in BMI from baseline to 16 weeks for a 2-group experiment (placebo versus liraglutide).

- Secondary Endpoint(s):
  There are 3 sets of key secondary endpoints:

  A. Changes in BMI and fat mass after 16 weeks of liraglutide.
  B. Comparison of changes in BMI and fat mass after 16 weeks liraglutide in participants who had a poor initial response to SG (<20% BMI reduction at BMI nadir) vs. those with a typical post-SG weight loss (≥20% BMI reduction at BMI nadir)
  C. Tolerability and safety of 3.0 mg Liraglutide

  Statistical hypothesis A: there will be a statistically significant decrease in BMI and fat mass after 16 weeks of liraglutide.

  Statistical hypothesis B: there will be a statistically significant greater decrease in BMI and fat mass after 16 weeks of liraglutide in participants in who had a typical post-SG weight loss vs. those who had a poor initial response to SG.

1.31 SAMPLE SIZE DETERMINATION

As this is a pilot investigation to determine the sample size of a fully powered investigation, no formal sample size determination is necessary. That said, the study is powered such that it might be able to detect a moderate-to-large difference from treatment. A recent randomized, double-blind, placebo-controlled phase 3 trial of liraglutide for adolescents (age 12 to <18 years) with obesity (BMI ≥30 kg/m^2 and ≥95th percentile for age and sex) [32] reported a -1.39 kg/m^2 (SE=0.31, n=125) difference over 1 year of liraglutide treatment. If that effect size is replicated and if a similar SD (3.46) is found in the present study, we estimate that a total sample size of 40 subjects will have 80% power (β) to detect a -1.39 kg/m^2 difference in BMI (effect size = -

0.4017) at level of significance of 0.05 (1-sided, as we are interested only in BMI loss). See **Table 2**.

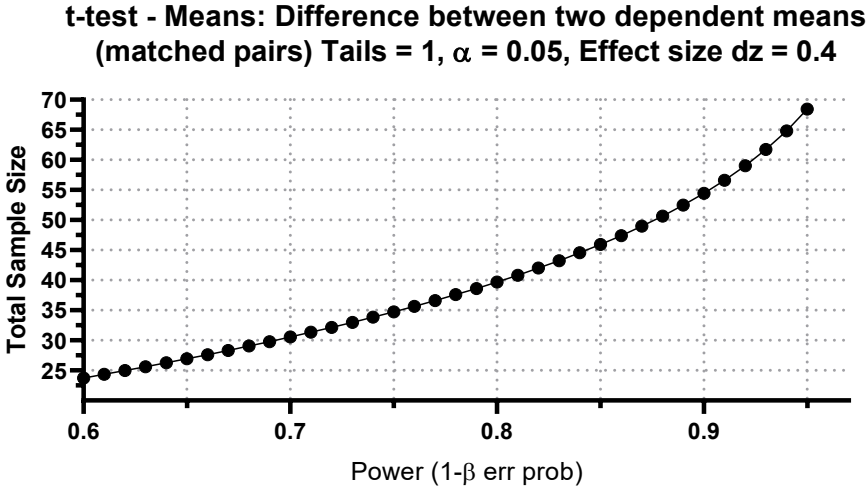


Table 2, drawn using data obtained using G-Power 3.1.9.2 [90, 91]

We anticipate that virtually all participants who sign consent and are screened will qualify and agree to enroll. We will therefore attempt to recruit and screen in person no more than 50 adolescents, among whom no more than 43 will be treated with liraglutide in hopes of having 40 who complete the study. Based on prior studies in adolescents using liraglutide, we anticipate few dropouts or withdrawals by week 16. In Kelly et al's study of adolescents [32], 119/125 (95%) of those treated with liraglutide remained on-treatment at week 16.

As a pilot investigation, there is no assumption that there will be adequate power for any of the secondary outcomes investigated. We will, however, be able to use the data to determine power in a future randomized controlled trial for these outcomes.

1.32 Populations for Analyses

The following analysis populations will be evaluated and used for presentation and analysis of the data:

- **Screening Analysis** Dataset: All participants who have a signed informed consent form.
- **Intention-to-Treat (ITT)** Analysis Dataset: all treated participants. The ITT Population will consist of all adolescent subjects who were assigned to treatment regardless of whether the subject received treatment or not. A subject is considered assigned to treatment when the Investigator or Investigator's designee assigns a medication study number. For all analyses in the ITT Population, participants will be analyzed as treated, whether or not treatment was received.
- **Safety Analysis** Dataset: the subset of participants for whom safety analyses will be conducted: Participants who took at least one dose of study medication will be considered part of the Safety Analysis Dataset.

- **Per Protocol** Dataset: Those who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of treatment according to the underlying scientific model (i.e., participants who took at least 80% of study intervention for 80% of the days within the treatment period).

1.32.1 Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment with liraglutide.

1.32.2 Evaluable for objective response

Not applicable

1.32.3 Evaluable Non-Target Disease Response

Not applicable

1.33 STATISTICAL ANALYSES

1.33.1 General Approach

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category of the parameter will be presented. For continuous variables, the number of subjects (N), mean, median, standard deviation (SD), minimum, and maximum values will be presented.

Formal statistical hypothesis testing will be performed on endpoints with testing conducted at the 1-sided, 5% level of significance. Summary statistics will be presented, as well as confidence intervals (Cis), as described in the sections below. Trial success will be based on a p-value <0.05.

Covariates to be modeled are pre-specified in the sections below. Results of statistical procedures for efficacy outcomes involving covariates will be presented as adjusted means (least-squares means) with standard errors.

Checks of assumptions (e.g., normality) underlying statistical procedures will be performed and corrective procedures will be applied. It is expected that log transformation will be used for the primary outcome and most secondary outcomes. Percentage data will be arcsin (square root (value)) transformed for analysis.

Unless otherwise noted, all statistical analyses will be performed using SPSS statistical software Version 25 (IBM Corp, Armonk, NY) or higher.

Subject disposition will be tabulated and include the number screened, the number randomized, the number treated in total, the number dosed with liraglutide, the number in each subject population for analysis, and the number who withdrew prior to completing the study and reason(s) for withdrawal.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be made available. Subject disposition will include patients in the Screening Analysis Dataset.

1.33.2 Analysis of the Primary Endpoint

The Primary Endpoint is estimation of required sample size for a later RCT through calculation of effect size for change in body mass index (BMI) from baseline to 16 weeks of liraglutide. The statistical hypothesis is: The data will be sufficient to calculate the effect size for change in BMI from baseline to 16 weeks for a 2-group experiment (placebo versus liraglutide). The primary outcome could be stated as the percentage of participants who are in the Per Protocol Dataset (who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of treatment according to the underlying scientific model (i.e., participants who took at least 80% of study intervention for 80% of the days within the treatment period). The study will be considered successful if more than 80% complete the trial.

The key variable that will be calculated is the effect size of the investigation. This value will be determined using the observed mean change in BMI from baseline to 16 weeks and the standard deviation for mean change observed with liraglutide treatment. The effect size (in this case, the Standardized Mean Difference (SMD) between two groups) will be calculated using Gpower 3.1.9.2 [90, 91] assuming the same standard deviation for both liraglutide-treated and control groups, a similar sample size for each group, and the observed difference in BMI from baseline to 16 weeks as the outcome of interest. Cohen's d – M_1-M_2)/SD_{pooled}. A plot will be created showing a range of sample sizes required for a between-groups t-test. For example, if we use the data from a recent randomized, double-blind, placebo-controlled phase 3 trial of liraglutide for adolescents who had not previously undergone bariatric surgery but had obesity [32], the liraglutide reduced BMI by -1.39 kg/m^2 (SE=0.31, n=125 over 1 year of treatment and the placebo group increased BMI by 0.19 kg/m^2 (SE=0.33, n=126) over the sample interval. If we found a similar reduction in BMI in adolescents who have obesity after bariatric surgery, the estimated effect size d=0.4566 (a difference of 1.58 kg/m^2 between groups with SD 3.46), a total sample size of 120 (60 per group) would be needed for one-sided α=0.05 and power of 0.80 (Table 1).

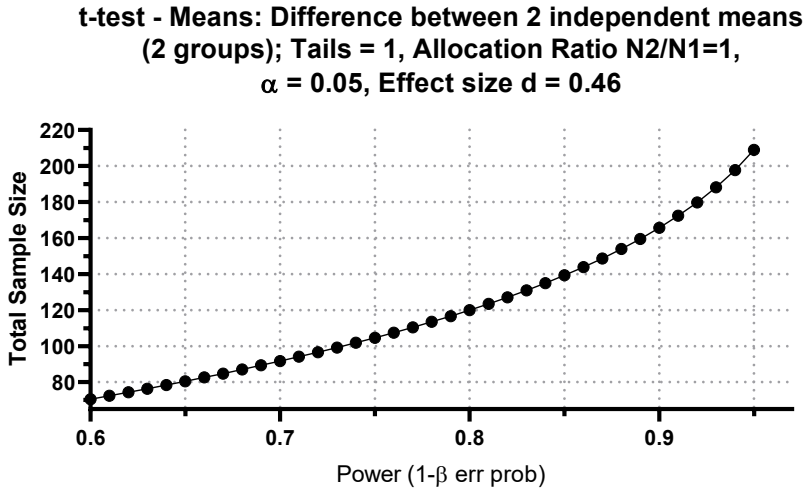


Table 1, drawn using data obtained using G-Power 3.1.9.2 [90, 91]

1.33.3 Analysis of the Secondary Endpoint(s)

There are 2 sets of key secondary endpoints. These analyses are not dependent on findings of the primary endpoint. They will be calculated as changes from baseline to 16-week visit in the ITT dataset:

1. Changes in BMI and fat mass after 16 weeks of liraglutide.
2. Comparison of changes in BMI and fat mass after 16 weeks of liraglutide in participants who had a poor initial response to SG (<20% BMI reduction at BMI nadir) vs. those with a typical post-SG weight loss (≥20% BMI reduction at BMI nadir)

For these analyses, last observation carried forward (LOCF) imputation will be used for missing data. The sample is too small to use any other statistical imputation method accurately. A sensitivity analysis using baseline observation carried forward (BOCF) will also be conducted.

Changes in BMI and fat mass after 16 weeks of liraglutide will be evaluated using paired t-tests of baseline versus 16-week values. Data will be transformed as necessary to meet statistical assumptions of normality.

Comparisons between those who had a poor versus typical post-SG weight loss will be conducted with ANCOVAs with change (16-week minus baseline value) as the dependent factor; group (poor vs. typical weight loss) as the independent factor; and sex, race, age, and height tested as potential covariates.

Tertiary endpoints will be evaluated using similar approaches. For the secretome analysis, paired statistical tests will be applied to each analyte (using parametric or nonparametric statistical approaches as required by the data) to find significant changes in secretome components. The Benjamini-Hochberg procedure will be used to determine the false discovery rate for multiple comparisons.

1.33.4 Safety Analyses

Safety endpoints will be analyzed as summary statistics during treatment in the Safety dataset. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses. AEs will be analyzed based on the drug received.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent AE (TEAE) is defined as an AE that starts or worsens at or during the time of or after the first study drug administration through the final visit. Each TEAE will be counted once only for a given participant. Severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC). For SAEs, information will be reported about start date, stop date, severity, relationship, expectedness, outcome, and duration. Adverse events leading to premature discontinuation from the study intervention and TEAEs will be presented in a table or a listing.

Clinical Laboratory Evaluations: All numeric laboratory data including chemistry (such as acute care panel and hematology tests will be summarized at each visit as well as changes from baseline using summary statistics. Laboratory values will be categorized as normal, high, and low, based on normal ranges. Shift from baseline will be summarized at each post-baseline visit.

Vital Signs: Descriptive statistics for resting heart rate, diastolic blood pressure, systolic blood pressure, temperature, and the change from baseline to each post-baseline visit. The change from baseline to the minimum and maximum post-baseline values will also be summarized by treatment group. Shift tables may also be presented. Clinically significant vital signs will be identified in the eCRF and will be listed.

1.33.5 Baseline Descriptive Statistics

Demographics and baseline characteristics will be summarized and presented. Age, height, weight, BMI, BMI-SDS, and fat mass percentage at study baseline will be summarized using descriptive statistics (N, mean, SD). The number and percentage of subjects in each sex, ethnicity, and race category also will be presented. Baseline HOMA-IR, fasting glucose and fasting insulin, as well as other measures of metabolism (e.g. cholesterol and triglycerides) will be summarized using descriptive statistics (N, mean, SD).

1.33.6 Planned Interim Analyses

No formal interim analyses are planned for safety, futility or efficacy.

1.33.7 Sub-Group Analyses

The sample size is too small to support meaningful sub-group analyses for age, sex, or race/ethnicity, and no such analyses will be conducted.

1.33.8 Tabulation of individual Participant Data

Individual participant data will not be listed by measure and time point.

1.33.9 Exploratory Analyses

Any of the exploratory evaluations that generate quantitative measures will be examined using descriptive statistics including confidence intervals when appropriate. Any statistical tests (paired t-tests of baseline versus 16-week results) performed for evaluation of exploratory objectives will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

The following dependent variables will be examined in the dataset:

> Change in: BMI standard deviation score for age and sex, body weight, percentage total body fat mass by DXA, appetite score using visual analog scale, attention bias to highly palatable images, energy intake at buffet meal, free living physical activity by accelerometry, hemoglobin A1C, plasma GI hormones (GLP-1 and PYY), weight related quality of life score, Beck depression inventory total score, Columbia-Suicide Severity Rating Scale, body-esteem scale score for adolescents and adults, HOMA-IR, fasting glucose and insulin, triglycerides, LDL- and HDL-cholesterol, OGTT glucose and insulin AUC, SomaScan platform.

REGULATORY AND OPERATIONAL CONSIDERATIONS

1.34 INFORMED CONSENT PROCESS

1.34.1 Consent/Assent Procedures and Documentation

In obtaining and documenting informed consent, all study staff will comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and will adhere to ICH GCP.

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 and Assent forms will be Institutional Review Board (IRB)-approved and the participant (and/or parent/guardian) will be asked to read and review the documents. The principal investigator or associate investigators with appropriate expertise will obtain written, active consent before the Screening Visit or as the first activity conducted at the Screening Visit. The purpose of the project, all testing procedures, and study components, and of their rights as research participants, will be described in detail in terms suited to the participant's comprehension. Potential participants and their parents will also be informed of the possible risks and inconveniences of the study. The investigator will answer any questions that may arise. The investigator will also explain the study assent form to minors using appropriate language. Sufficient time and opportunity will be given for discussion of the research as well as to answer any questions all may have, taking care to minimize or eliminate the perception of coercion or undue influence.

Participants will have the opportunity to carefully review the written consent form and ask questions before signing. The participants will have the opportunity to discuss the study with their family or surrogates and given time to think about it prior to agreeing to participate. The participant (or parent/guardian) will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. 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. The informed consent form (and assent if applicable) will be signed before the participant undergoes any study-specific procedures. The investigator-designated research professional obtaining the consent (and assent if applicable) must also sign the informed consent and assent form (if applicable). A copy of the informed consent/assent documents will be given to the participants for their records. The informed consent process will be documented in the medical record (including the date), and the original completed forms will be kept in the participant's medical record with a copy in their research chart.

Informed consent documents (and assent documents, if applicable) may be printed to sign and date in ink, or the electronic documents may be signed with a hand signature using a finger, mouse or stylus via an approved platform. Participants may be asked to complete the consent process electronically via iMed and Docusign, which are both 21 CFR Part 11 compliant. Once identity is confirmed, consents can be electronically signed, date-stamped, and routed to the PI for electronic signature. Once the PI has logged into the secure site and digitally signed the consent, a pdf of the signed consent is created. As is done for forms signed in ink, the participant will be provided with a copy of the signed document, and can also contact our study staff to obtain a hard copy of the consent at any point in this process.

For assent of children

All adolescent participants are expected to be able to comprehend and be included in all discussions about the trial. Age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts, and benefits of participation. All child study participants, who will be between age 12 and <18 years will be asked to sign an age appropriate assent form. The consent/assent process will be documented in the child's medical record. All children will be contacted after they have reached the age of 18y to determine whether they wish to continue participating in the trial; informed consent will be obtained from them at that time.

Telephone consent

In certain instances, the PI or designee will obtain informed consent by a telephone or video conversation with a protocol-eligible subject who cannot travel to the NIH Clinical Center for a considerable period of time. A parent/guardian will be involved if the subject is <18 years of age.

The informed consent document will be sent to the subject by mail, email, or fax. An explanation of the study will be provided over the telephone or other electronic media (via an NIH approved remote platform) after the subject has had the opportunity to read the consent form. The informed consent form will be signed and dated.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was returned.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator.

The investigator will confirm that, when required, written legally effective consent has been obtained prior to initiating any study interventions.

Telephone assent

The informed consent and assent documents will be sent to the parents/guardian and child. An explanation of the study will be provided over the telephone after the parents/guardian and child have had the opportunity to read the documents. Age-appropriate language will be used to discuss the study with the child. The parents/guardian will sign and date the informed consent. The child will sign and date that form. All children will be contacted after they have reached the age of 18y to determine whether they wish to continue in the trial and informed consent will be obtained from them at that time.

The original signed informed consent and assent documents will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was returned.

A fully executed copy will be returned via mail to the subject.

The informed consent and assent process will be documented on a progress note by the consenting investigator.

1.34.2 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require that consent be obtained from the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained.

If reconsent is not feasible, we request waiver of informed consent to continue to use data and/or specimens for those individuals who become lost to follow up or who have been taken off study prior to reaching the age of majority.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.
(3) As the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

    a. Though the purpose of future studies cannot yet be known, they often involve the correlation of clinical outcomes and clinical interventions with laboratory studies. Such information would be unavailable if access to medical record numbers was unavailable.
(4) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.
(5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
    a. We only request a waiver of consent for those subjects who have been lost to follow-up or who have been taken off study prior to reaching the age of majority.

1.34.3 Consent of Subjects who are, or become, decisionally impaired

Not applicable. Adults unable to provide consent are excluded from enrolling in the protocol. However, it is possible that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. In the event this occurs, the subjects will be withdrawn from the study.

1.35 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 study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and NICHD Clinical Director 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
- 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 NICHD Clinical Director, IRB and, as applicable, the Food and Drug Administration (FDA).

1.36 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests 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 Principal Investigator.

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

The study monitor, other authorized representatives of the NICHD Clinical Director, representatives of the Institutional Review Board (IRB), and/or regulatory agencies 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 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 NICHD requirements. Samples and data will be coded. Human biospecimens will be collected using procedures appropriate for the type of biospecimen being collected and will be handled in accordance with the U.S. Occupational Safety and Health Administration's Bloodborne Pathogens Standard for Samples. The principal investigator and the co-investigators will have access to identifiable participant records. Data will be coded by subject number but will be readily associated with identifiable participant records. Records containing personal identifiers will be maintained consistent with the security measures required by the NIH. All NIH data will be kept on secure computers in the SGO office, whose doors will be locked when staff is not present. All paper data will also be kept in locked areas in the SGO office. Serum and plasma samples not analyzed

immediately (as described above) NIH will be stored indefinitely in locked freezers by the NICHD sample management team supervised by the NICHD Clinical Director and tracked/managed through the NICHD Clinical Trials Database (CTDB). Human biospecimens in NICHD storage will have a unique identifier, will be labeled with a printed label and will contain a barcode. Samples will be tracked using a computer-based inventory system that records the location and detailed information of every specimen in the repository

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in CTDB. 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 research staff will be secured and password protected.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

1.37 FUTURE USE OF STORED SPECIMENS AND DATA

Stored samples, specimens or data may be sent to collaborators for specific measurements or analyses. All stored samples, specimens, and data will be coded so that when sent for measurements the identity of the volunteer remains confidential. Identification of coded samples will be kept in a secure, password-protected database accessible only to investigators, but will be identifiable in case specific tests yield clinical information of importance to a particular volunteer or samples can be destroyed per volunteer request (see below). Samples will be used only for research and not for commercial purposes. Research volunteers will not be informed of individual results from analyses performed specifically for research purposes, unless there is clear evidence accepted by the medical community that these results would impact the volunteer's individual medical care or future health. Samples will be stored until used and will not be destroyed unless specifically requested in writing by the volunteer.

Additional consent will be obtained to use samples for purposes not already specified if participants have requested such consent be obtained (see consent form). Prior to transfer of samples and data to other (additional) non-NIH collaborators, a material transfer agreement (MTA) with the outside institution will be established. The PI will provide the IRB with a listing of MTA's that have been established under these provisions at the time of the Continuing Review and include a record of each such collaboration in the study protocol.

Staff will report to the Principal Investigators any destroyed samples, if samples become unsalvageable because of environmental factors (ex. Broken freezer or lack of dry ice in a shipping container), lost in transit between facilities or misplaced by a researcher. The PI will record any loss or unanticipated destruction of samples as a deviation.

1.38 SAFETY OVERSIGHT

The clinical research team will meet on a weekly basis when participants are being actively treated on the trial to discuss progress and adverse events. All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Events meeting requirements for expedited reporting will be submitted within the appropriate timelines.

Safety oversight will be under the direction of a Clinical Safety Officer (CSO) who is a Licensed Independent Practitioner (LIP) with relevant clinical experience. The CSO will be independent and not otherwise involved in the conduct of the trial. The NICHD Clinical Director and the Director of Clinical Research and Compliance, or their designees, will approve the selected CSO. The CSO and the PI will jointly determine an interval for routine safety monitoring appropriate for the risk level of the trial. This will be included as part of the monitoring plan in the clinical study protocol along with appropriate study stopping rules. The PI is responsible for promptly notifying the CSO of any emerging safety signals. The CSO will review all Dose-Limiting Toxicities (DLTs) considered to be at least possibly related to the study drug, instances of dose reductions due to intolerability, as well as any emerging safety signals identified by the PI on an ad hoc basis. All Adverse Events, including those that are expected, will be described in the routine safety monitoring reports reviewed by the CSO. If there are unresolved differences regarding adverse event causality assessment, event reporting, or management, the NICHD Clinical Director and the Director of Clinical Research and Compliance, or their designees, will be notified and asked to adjudicate. The CSO will provide its input to the Clinical Director of NICHD and other staff as appropriate.

For this pilot study of a medication that is FDA-approved for the age group investigated, that is performed under an FDA exemption, it is anticipated that the chance of unexpected AEs that would lead to study discontinuation is low. Therefore, it is proposed that the routine report that the CSO will review that includes all AEs will occur once yearly, at the time of Continuing Review. As specified above, SAEs will be reported promptly to the CSO independent of this scheduled report.

After half of all anticipated subjects (i.e. at n=20) have had the opportunity to take study medication for the 16-week treatment period, the CSO will review the percentage of enrolled subjects who continued to take study medication through the 16 week (primary efficacy) timepoint. If fewer than 50% remain in the per protocol dataset, the study will be stopped.

The study will also be reviewed to determine if it should be stopped if 3 or more study subjects develop unexpected SAEs that are assessed as probably related to study medication or if 6 or more study subjects develop expected or unexpected SAEs that are assessed as probably related to study medication.

Individual study subject stopping rules have also been established (see attached file titled, “CTCAE_v5.0_2017-11-27 for Liraglutide - revised 2021-FEB-24”. In general, a participant will at a minimum reduce the dose and, in most instances, not continue study medication if they develop CTCAE 5 grade 3 or greater adverse events, but in some categories lower grades will lead to consideration of medication discontinuation.

1.39 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 Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Auditors from the Office of the Clinical Director, NICHD or a designated contracted organization will conduct the monitoring on-site. Initial review will occur as soon as possible after IRB approval for initial assessment and training. Monitoring will then continue at a minimum annually but more frequently if needed, with yearly targeted review of 50% or more of participant's data, for the purpose of verification of primary and secondary endpoint values, laboratory safety reports (hematology and chemistry), CRF completeness, consent/assent signatures, annual submission of Continuing Review and FDA IND reports, and for accuracy of data transcription into the study database. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, NICHD.

1.40 QUALITY ASSURANCE AND QUALITY CONTROL

The 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 will be applied at each stage of data handling to ensure that all data are reliable and have been processed (e.g., monitoring to review source documents/subject's charts against eCRFs, development of a monitoring plan, data management system with appropriate logic checks, quality control review of the database prior to database lock, quality control procedures to confirm accurate table, listings, etc.). 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 for clarification/resolution.

Audits will be performed as part of implementing quality assurance. Audits will evaluate study conduct, data/record integrity, and/or compliance with the protocol, standard operating procedures, GCP, and applicable regulatory requirements. 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 Conference 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 NICHD, and inspection by local and regulatory authorities.

1.41 DATA HANDLING AND RECORD KEEPING

1.41.1 Data Collection and Management Responsibilities

Medical and research records for this trial will be maintained in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH-sponsored study, the site will permit authorized representatives of the NIH, NICHD, and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity

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.

Hard copies of the 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 NICHD Clinical Trials Database, a 21 CFR Part 11-compliant data capture system. 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. Clinical notes from each visit will also be recorded in the NIH CRIS system.

1.41.2 Study Records Retention

Upon completion of the study Jack A. Yanovski, MD, PhD will retain possession of the electronic IND binder and electronic Protocol Binder in a secure location. Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference 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, and as per the NIH Intramural Records Retention Schedule. No records will be destroyed without the written consent of the sponsor, if applicable.

1.42 PROTOCOL DEVIATIONS AND NON-COMPLIANCE

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or non-compliance to the NIH Institutional Review Board as per Policy 801. All deviations must be addressed in study source documents, reported to the NICHD Clinical Director. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

1.42.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

1.43 PUBLICATION AND DATA SHARING POLICY

1.43.1 Human Data Sharing Plan

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

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 1 year after the completion of the primary endpoint by contacting Dr. Yanovski.

This study involves the collection of human data in the form of anthropometric (e.g., DXA, BMI), metabolic (e.g. blood glucose and insulin), and drug tolerability (e.g., adverse event) data. After obtaining consent for data sharing, de-identified data will be made available without cost to researchers and analysts through government-supported publicly accessible databases, or a similar publicly available databases for which user registration is required. Data will be made available proximately following publication of findings that address the main and secondary aims of the protocol and will include the relevant phenotypic data. Users must agree to the conditions of use governing access to the public release data, including limitation of research to investigations consistent with the participants' consent, restrictions against attempting to identify study participants, destruction of the data after analyses are completed, reporting responsibilities, restrictions on redistribution of the data to third parties, and proper acknowledgement of the data resource.

What data will be shared?

- We will share human data generated in this research for future research as follows: Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

- Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository: clinicaltrials.gov.
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations

1.43.2 Genomic Data Sharing Plan

Not applicable

1.44 COLLABORATIVE AGREEMENTS

Not applicable

1.44.1 Agreement Type

Not applicable

1.45 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, 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 in conjunction with the NICHD 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.

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
BMIz	Body Mass Index Standard Deviation Score for age and sex
BOCF	Baseline Observation Carried Forward
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CNH	Children's National Hospital
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DXA	Dual-Energy X-ray Absorptiometry

DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GI	Gastrointestinal
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GLP-1	Glucagon-Like Peptide 1
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LOCF	Last Observation Carried Forward
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
OGTT	Oral Glucose Tolerance Test
PI	Principal Investigator
PYY	Peptide YY
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RCT	Randomized Controlled Trial
RYGB	Roux-en-Y gastric bypass
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SG	Sleeve Gastrectomy
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
VAS	Visual Analog Scale

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