University of Minnesota

Enhancing Weight Loss with Medication in Adolescents

Regulatory Sponsor:	University of Minnesota
Funding Sponsor:	National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Study Product:	Exenatide extended-release for injectable suspension (BYDUREON™)
IND Number:	126745
Principal Investigator:	Aaron S. Kelly, Ph.D.
Medical Officer/Co-Investigator:	Claudia K. Fox, M.D., M.P.H.
Co-Investigators:	Kyle D. Rudser, Ph.D. Brandon M. Nathan, M.D. Amy Gross, Ph.D., L.P. Muna Sunni, M.B.B.Ch. Charles Billington, M.D. M. Jennifer Abuzzahab, M.D. Seema Kumar, M.D. Betsy Schwartz, M.D. Justin R. Ryder, Ph.D. Donald R. Dengel, Ph.D. Megan Oberle, M.D.
Version Date:	Version 7, 13 November 2019

Protocol Change History:	Version 1: 13 May 2015 Version 2: 18 August 2015: Addition of FDA stipulated safety measures Version 3: 15 October 2015: Addition of Fairview stipulated recruitment language Version 4: 11 April 2016: duration of Phase 1 reduced to 8 weeks (from 12 weeks) Version 5: 07 December 2017: clarifications regarding baseline lab, exclusion criteria; removal of vascular measures; substance abuse and neuromuscular disorder exclusion Version 6: 25 June 2019: Corrects a typographical error regarding the number of subjects to be enrolled. Version 7: 13 November 2019: Adds the PHQ-2 as a safety measure to be done at every in-person visit. The PHQ-2 was developed to help identify depressed mood and anhedonia, and following changes in depression could be helpful in this population. The protocol also adds in an action plan for individuals who have a score of 3 or greater.

Table of Contents

List of Abbreviations

AE	Adverse Event
AEBQ	Adult Eating Behavior Questionnaire
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
AUC	Area-under-the-curve
BMI	Body mass index
CEBQ	Child Eating Behavior Questionnaire
CES-DC	Depression Scale for Children
CFR	Code of Federal Regulations
CIs	Confidence intervals
CLIA	Clinical Laboratory Improvement Amendments
CPAP	Continuous Positive Airway Pressure
BIPAP	Bilevel Positive Airway Pressure
CRF	Case Report Form
CTSI	Clinical Translational Science Institute
DSMB	Data safety and monitoring board
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HDL	High density lipoprotein
IDS	Investigational Drug Services Pharmacy
iDXA	i Dual Energy X-ray Absorptiometry
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to Treat
LDL	Low density lipoprotein
PHI	Personal Health Information
PHQ-2	Patient Health Questionnaire-2
REPA	Report of External Professional Activities
SAE	Serious Adverse Event
UPIRTSO	Unanticipated problems involving risk to subjects or others

Study Summary

Title	Enhancing Weight Loss with Medication in Adolescents
Phase	Phase 3
Methodology	Randomized, double-blind, placebo-controlled clinical trial
Study Duration	5 Years
Study Center	University of Minnesota in collaboration with the Minnesota Pediatric Obesity Consortium (MN-POC)
Objective & Hypothesis	**Primary Objective: Evaluate the effect of glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment on the maintenance of weight loss and durability of cardiometabolic risk factor improvements among adolescents with severe obesity following a meal replacement induction period.** We hypothesize that adolescents with severe obesity receiving GLP-1RA treatment following a short-term meal replacement induction period will demonstrate superior maintenance of initial BMI reduction 52 weeks following randomization compared to those assigned to placebo (primary endpoint) and that a higher proportion of those assigned to GLP-1RA treatment vs. placebo will maintain ≥5% BMI reduction from baseline to the 52-week time point (secondary endpoint). Moreover, GLP-1RA treatment will result in superior maintenance of initial reductions of body fat (total, visceral, and subcutaneous), blood pressure, triglycerides/HDL ratio, inflammation, oxidative stress, postprandial glucose-insulin response, insulin resistance, and β cell dysfunction at 52 weeks. **Secondary Objectives: Investigate the mechanisms by which GLP-1RA treatment facilitates weight loss maintenance and identify predictors of response to treatment.** We hypothesize that compared to placebo, GLP-1RA treatment following a period of meal replacement will reduce appetite (and related hormones) and gastric emptying rate, and will increase satiety (and related hormones) and resting energy expenditure at 26- and 52 weeks following randomization. Moreover, based on our preliminary work, we hypothesize that appetite (and appetite-related hormones) following the meal replacement period and female gender will be associated with superior weight loss maintenance with GLP-1RA treatment.
Number of Subjects	We anticipate having to consent/screen up to 250 subjects.
Diagnosis and Main Inclusion Criteria	**Diagnosis:** Severe obesity **Main Inclusion Criteria:** • BMI ≥1.2 times the 95th percentile (based on sex and age) or BMI ≥35 kg/m^2 • Age 12-17 years

Study Product, Dose, Route, Regimen	**Study Product (dose and route)** Exenatide extended-release for injectable suspension (BYDUREON™) 2.0 mg weekly **Regimen** After achieving ≥5% BMI reduction during a run-in period of up to 8 weeks of meal replacement therapy, participants will be randomly assigned to exenatide or matching placebo for a subsequent period of 52 weeks.
Statistical Methodology	The primary analysis will be conducted using the intent-to-treat population to compare the mean BMI percent change from randomization to 52 weeks of follow-up between exenatide and placebo groups, adjusted for randomization values of BMI. Confidence intervals and P-values will be based on robust variance estimation. Statistical significance will be considered as $p<0.05$.

1 Introduction/Summary

Long-term weight loss maintenance is seldom achieved by individuals with obesity owing to numerous biological adaptations involving appetite, satiety, and energy expenditure in the post-weight loss setting. Following a loss in body weight, peripheral and central mechanisms convey a sense that energy reserves have dwindled, activating a strong counter response to increase caloric intake. Adolescents with severe obesity are not immune to the vexing issue of weight regain. Indeed, only 2% are able to achieve and maintain clinically-meaningful weight loss with lifestyle modification therapy. Therefore, novel treatment paradigms focused on long-term weight loss maintenance are urgently needed. Pharmacotherapy has the potential to prevent weight regain by targeting specific counter-regulatory mechanisms in the post- weight loss setting. One of the most promising candidates is the glucagon like peptide-1 receptor agonist (GLP-1RA) class, which greatly enhanced weight loss maintenance following a short-term low calorie diet among adults with obesity. The rationale for focusing on GLP-1RA treatment to prevent weight regain is supported by the multiple central and peripheral mechanisms of action targeted by this class of drug; many of which specifically address the biological adaptations known to induce relapse. We have strong preliminary data demonstrating that GLP-1RA treatment reduces BMI in adolescents with severe obesity. Moreover, we and others have shown that although meal replacement therapy (structured meals of known caloric content) can elicit robust short-term weight loss among adolescents with severe obesity, weight regain is a pervasive problem. Therefore, in this clinical trial, our innovative approach will utilize GLP-1RA treatment to target weight regain following short-term meal replacement therapy in youth with severe obesity. Participants who achieve ≥5% BMI reduction during the meal replacement phase will be randomized to GLP-1RA treatment or placebo for an additional 52 weeks while simultaneously engaging in lifestyle modification therapy. Importantly, this study will also allow us to examine the extent to which GLP-1RA treatment addresses mechanisms of weight regain, investigate other pleiotropic benefits of GLP-1RA, and identify predictors of weight loss response.

1.1 Background and Rationale

Obesity is a chronic disease requiring lifelong management. Long-term weight loss maintenance is seldom achieved by individuals with obesity owing to numerous biological adaptations involving appetite, satiety, and energy expenditure in the post- weight loss setting.[1-3] Following a loss in body weight, peripheral and central mechanisms convey a sense that energy reserves have dwindled, activating a strong counter response to increase caloric intake.[2] Moreover, resting and non-resting energy expenditure decreases, further compounding the propensity for weight rebound.[1] Adolescents with severe obesity (BMI ≥1.2 times the 95th percentile or BMI ≥35 kg/m^2) are not immune to the vexing issue of weight regain as evidenced by the poor outcomes of interventions using lifestyle modification alone.[4-7] Indeed, only 2% of adolescents with severe obesity are able to achieve and maintain clinically-meaningful weight loss with lifestyle modification therapy.[4] These findings are sobering considering the relatively high prevalence of pediatric severe obesity (8% in the United States), the rate at which it is increasing (fastest growing category of obesity), and the serious immediate- and long-term medical and psychosocial consequences of the disease.[8, 9]

The number and levels of cardiovascular risk factors are considerably higher in severe pediatric obesity compared to those associated with milder forms of obesity. Approximately 85% of children and adolescents with severe obesity have at least one cardiovascular risk factor and 60% have two or more.[10] Subclinical atherosclerosis and arterial stiffening in the carotid artery is present in youth with severe obesity at levels similar to peers with type 2 diabetes.[11]

Compared to overweight and obese peers, youth with severe obesity have higher levels of inflammation and oxidative stress,[12] an adverse adipokine profile,[13] and arterial endothelial activation.[14] Moreover, longitudinal data uniformly implicate obesity in childhood as a strong predictor of future risk factor clustering and sub-clinical atherosclerosis in adulthood.[15-17] Risk of developing type 2 diabetes is high in youth with severe obesity.[18-26] The prevalence of impaired glucose tolerance in children and adolescents with severe obesity is notable, with estimates ranging from 4.5%-25%.[27-29] Perhaps most alarming is the poor prognosis for youth afflicted with severe obesity. Approximately 90% will have a BMI ≥35 kg/m^2 in adulthood;[10] and severe obesity in adulthood reduces life expectancy by 7-14 years.[30] Considering the serious nature of the disease, the poor efficacy of lifestyle modification approaches when used alone, and the higher level of risk associated with bariatric surgery, a new direction must be taken in the treatment of severe obesity in adolescents. If the field is to move forward, novel treatment paradigms focused on long-term weight loss maintenance and the incorporation of pharmacotherapy need to be explored.

Pharmacotherapy has the potential to prevent weight regain by targeting specific counter-regulatory mechanisms in the post- weight loss setting, and various agents have improved long-term weight loss durability in studies of adults.[31-34] One of the most promising strategies involves the use of the GLP-1RA class of medication, which was originally approved by the FDA for use in adults with type 2 diabetes to improve glycemic control (weight loss is a beneficial "side effect") and was recently approved for a weight loss indication. Recently, GLP-1RA treatment was shown to greatly enhance weight loss maintenance (and produced additional weight loss) following a short-term low calorie diet among adults with obesity.[34] Over 80% of those treated with GLP-1RA maintained ≥5% weight loss at one year.[34] The rationale for specifically focusing on the GLP-1RA class to prevent weight regain is the multiple central and peripheral mechanisms of action addressed by the drug, which target many of the post- weight loss counter-regulatory biological adaptations known to induce relapse by: 1) reducing appetite through activation of GLP-1 receptors in the hypothalamus; 2) enhancing satiety by slowing gastric emptying and bolstering the vagal afferent signaling of gastric distension to the nucleus tractus solitarius portion of the hind brain; 3) beneficially altering insulin and leptin signaling in the hypothalamus and amygdala and inhibiting the reward pathways associated with hedonic eating behaviors; and 4) increasing energy expenditure.[34-46] Through these various mechanisms, sustained weight loss has been achieved in the long-term (at least two years) using GLP-1RA treatment in adults.[47] Additional justification for using this specific class of medication in adolescents with severe obesity includes recent evidence showing that GLP-1 levels are reduced in the context of pediatric obesity,[48] indicating a potentially maladaptive response in some individuals. Moreover, GLP-1RAs, via weight loss dependent- and -independent mechanisms, improve many obesity-associated risk factors and co-morbidities such as impaired glucose tolerance, insulin resistance, hypertension, vascular dysfunction, and inflammation.[49-53]

We have preliminary data demonstrating that GLP-1RA treatment reduces BMI and improves cardiometabolic risk factors in adolescents with severe obesity.[50, 54] Moreover, we and others[55] have shown that although short-term meal replacement therapy (structured meals of known caloric content) results in clinically-meaningful weight loss (6% BMI reduction) among adolescents with severe obesity, weight regain is experienced by the vast majority of individuals and long-term weight loss maintenance is poor. The proposed clinical trial will take the next step and evaluate the weight loss-maintenance effectiveness of GLP-1RA treatment instituted immediately following a short-term meal replacement induction period among adolescents with severe obesity. Importantly, this study will also allow us to: 1) examine the extent to which GLP-1RA treatment targets the various mechanisms responsible for weight regain (including tracking

serial changes in a panel of appetite and satiety hormones), 2) investigate additional pleiotropic (weight loss-dependent and -independent) benefits of GLP-1RA therapy, and 3) identify predictors of successful weight loss maintenance with GLP-1RA treatment among adolescents with severe obesity.

1.2 Investigational Agent

Exenatide
Exenatide is a 39-amino acid synthetic peptide amide with an empirical formula of C184H282N50O60S and a molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown below.

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

1.3 Clinical Data to Date

Significance and Preliminary Work
The significance of the proposed work lies in the seriousness and prevalence of the disease being targeted (pediatric severe obesity) and the improved outcomes that we hope to deliver (durable weight loss and risk factor management) in this population in need of safe, effective, and durable treatments. The nature of severe obesity demands that appropriately-intensive interventions be initiated earlier in life, not later in adulthood when adiposity and co-morbidities have become entrenched. Therefore, investigation into promising non-surgical treatments for pediatric severe obesity is desperately needed, considering the risks of surgery are not inconsequential[56] and most will be unwilling to undergo this extreme treatment. Weight regain continues to be a major hurdle in the field of obesity medicine.

Study #1: Pilot and Feasibility Trial of GLP-1RA Treatment in Severe Pediatric Obesity[50]
We conducted a pilot and feasibility trial to evaluate the effects of the GLP-1RA exenatide on BMI (primary endpoint), cardiometabolic risk factors, and glucose tolerance in adolescents with severe obesity.[50] Twelve adolescents (ages 9-16 years old) were recruited from MN-POC sites and enrolled in a 6-month, randomized, open-label, crossover, clinical trial consisting of two, 3-month phases: 1) a control phase of lifestyle modification and 2) a drug phase of lifestyle modification plus exenatide. Participants were randomized to phase-order (i.e., starting with control or drug therapy) then crossed-over to the other treatment. Outcomes were assessed at baseline, 3-, and 6-months. Results are shown in Table 1. Compliance with the injection regimen was excellent (≥94%) and exenatide was generally well-tolerated. The most common adverse event was nausea, which was experienced in 4/11 (all classified as mild). Vomiting (3/11) and headache (3/11) were the second most common adverse events (all categorized as mild). The encouraging preliminary findings (BMI reduction of 5% and improvements in glucose tolerance, insulin sensitivity, and beta cell function) prompted our group to conduct a follow up trial (see “Study #2”, below).

Table 1. Three-Month Treatment Effects Within and Between Study Arms

Outcome	Δ Control	Δ Exenatide	Treatment Effect (95% CI)	P-value
BMI (kg/m^2)	0.84 (1.28)	-0.90 (1.22)	-1.71 (-3.01, -0.42)	**0.010**
Percent Change BMI	1.72 (4.19)	-2.57 (3.46)	-4.92 (-8.61, -1.23)	**0.009**
Weight (kg)	2.97 (2.88)	-0.99 (2.90)	-3.90 (-7.11, -0.69)	**0.017**
Body Fat (%)	0.92 (2.75)	-0.36 (3.07)	-1.28 (-4.66, 2.09)	0.457
SBP (mmHg)	3.10 (8.72)	-3.11 (8.51)	-5.31 (-14.89, 4.27)	0.277
HDL (mg/dL)	-0.20 (6.84)	3.44 (3.40)	3.25 (-2.47, 8.97)	0.266
Triglycerides (mg/dL)	-4.22 (37.45)	-9.89 (41.24)	-12.57 (-59.41, 34.28)	0.599
Glucose (mg/dL)	1.60 (6.40)	3.22 (5.85)	1.68 (-3.65, 7.01)	0.537
Glucose AUC (per 100)	11.69 (29.50)	-17.67 (22.98)	-27.96 (-56.51, 0.59)	**0.055**
Insulin (mU/L)	6.00 (5.58)	-1.62 (8.42)	-7.54 (-13.71, -1.37)	**0.017**
Insulin AUC (per 100)	30.29 (98.76)	-38.95 (73.74)	-76.01 (-166.30, 14.28)	**0.099**
WBISI/Matsuda	-2.00 (3.52)	4.12 (7.10)	6.13 (1.01, 11.25)	**0.019**
β-Cell Function	-1.16 (6.33)	14.50 (26.09)	17.97 (1.40, 34.54)	**0.034**

Values presented are mean (SD).

Study #2: Randomized, Placebo-Controlled, Multicenter Trial of GLP-1RA Treatment in Adolescents with Severe Obesity[54]

We performed a larger study with a more rigorous design (randomized, double-blind, placebo-controlled trial with a three-month open label extension) to evaluate the effects of exenatide on BMI and cardiometabolic risk factors in adolescents with severe obesity.[54] Twenty-six adolescents (age 12-19 years) were enrolled. All patients received lifestyle modification counseling and were equally randomized to exenatide or placebo injection, twice per day. The primary endpoint was the mean percent change in BMI measured at baseline and three-months. Twenty-two patients completed the trial. Results are shown in Figure 1 and Table 2.

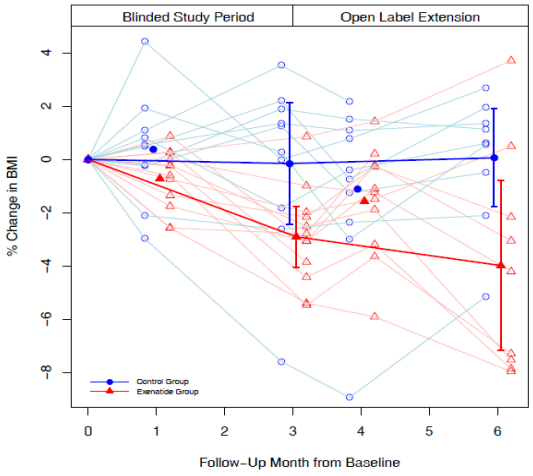


Figure 1. Percent Change in BMI during the Randomized, Placebo-Controlled and Open Label Phase

Of note, during the open label extension, BMI was further reduced in those initially randomized to exenatide (cumulative BMI reduction of 4%). Compliance was excellent and ranged from 85-100% of the required doses; mean = 95%. The most common adverse events (all mild-moderate and transient) were nausea (placebo 31%, exenatide 62%), abdominal pain (placebo 23%, exenatide 15%), diarrhea (placebo 31%, exenatide 8%), headache (placebo 46%, exenatide 23%), and vomiting (placebo 8%, exenatide 31%). The findings of this pilot trial provide additional evidence supporting the feasibility, safety, and efficacy of GLP-1RA treatment in adolescents with severe obesity.

Table 2. Change from Baseline to Three-Month Follow-up for Primary and Secondary Endpoints

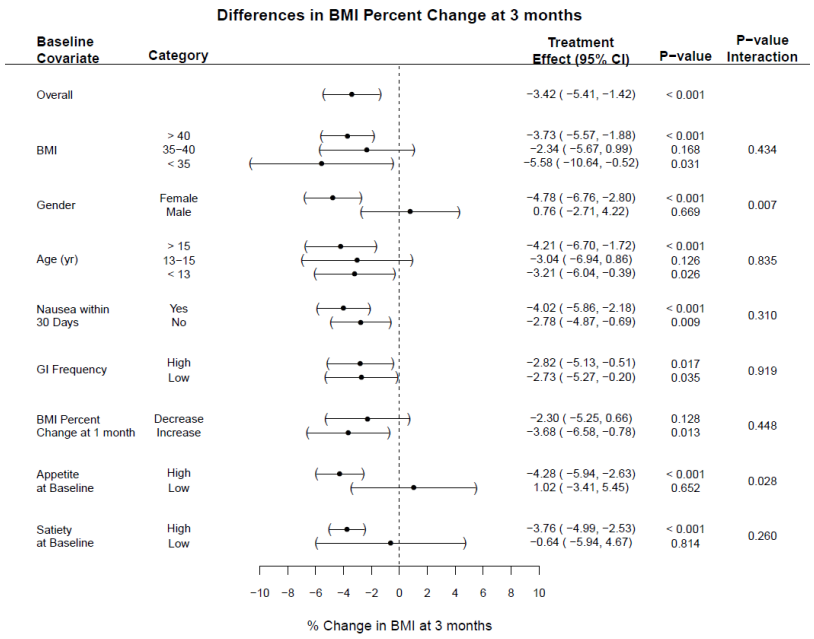
Covariate	N	Exenatide Δ	Control Δ	Estimate (95% CI)	P-value
Percent Change BMI	22	-2.90 (1.80)	-0.15 (3.20)	-2.70 (-5.02, -0.37)	**0.025**
BMI (kg/m^2)	22	-1.18 (0.67)	-0.04 (1.23)	-1.13 (-2.03, -0.24)	**0.015**
Weight (kg)	22	-2.93 (2.48)	0.32 (3.21)	-3.26 (-5.87, -0.66)	**0.017**
Waist (cm)	22	-2.04 (2.62)	-1.01 (5.57)	-0.98 (-4.60, 2.64)	0.579
Total Tissue Fat (kg)	15	-1.69 (2.41)	-0.65 (2.50)	-0.72 (-3.66, 2.23)	0.610
Visceral Fat Area (cm^2)	14	-97.00 (191.22)	-18.17 (178.62)	-78.15 (-309.55, 153.25)	0.473
SBP (mmHg)	22	-5.50 (9.13)	2.00 (13.43)	-6.36 (-13.46, 0.73)	**0.076**
HDL-cholesterol (mg/dL)	22	-0.42 (4.08)	-3.00 (5.12)	2.08 (-1.82, 5.99)	0.278
Triglycerides (mg/dL)	22	2.83 (53.69)	3.90 (44.41)	-4.71 (-45.14, 35.72)	0.810
Glucose (mg/dL)	22	1.17 (8.19)	4.60 (9.51)	-3.33 (-9.71, 3.05)	0.288
Insulin (mU/L)	22	-8.33 (18.81)	0.67 (7.43)	-2.91 (-10.91, 5.10)	0.455
HbA1c (%)	22	-0.12 (0.16)	-0.01 (0.14)	-0.11 (-0.23, 0.01)	**0.072**

Values presented are mean (SD).

<u>Study #3: Predictors of BMI Response with GLP-1RA Treatment in Adolescents with Severe Obesity (unpublished data)</u>

We pooled data from our previously-described pilot trials and evaluated whether specific factors would predict BMI reduction at 3 months. Data from the 29 participants who had a 3-month BMI measurement (mean age 14.5 ± 2.0 years; 66% female; mean BMI 40.2 ± 5.7 kg/m^2) were included. The primary predictor variables of interest were appetite and satiety at baseline from a validated questionnaire (Child Eating Behavior Questionnaire: CEBQ) modified to a self-report format for adolescents. Appetite (or "Food Responsiveness" from the CEBQ) and satiety (or "Satiety Responsiveness" from the CEBQ) were classified as high or low based upon a cut-point of 2.5 on the scale of 1-5 which ranges from "never" to "always" for each item mean. Additional exploratory predictor variables assessed included: baseline BMI, gender, age, early incidence (1 month) of nausea, GI symptom frequency, and BMI percent change at 1 month.

Figure 2. Predictors of BMI Response with GLP-1 RA Treatment

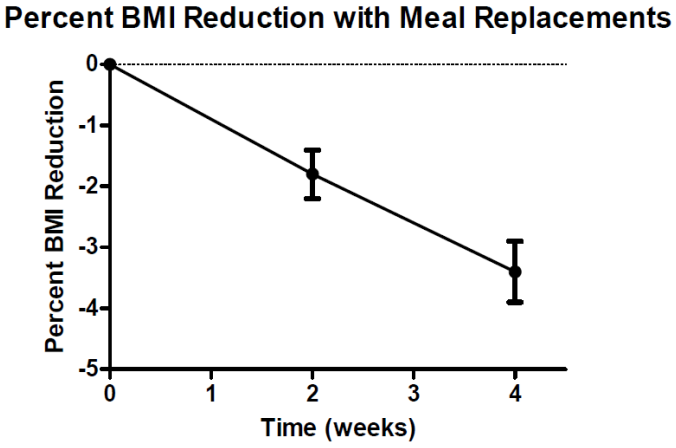


Mean differences in percent change in BMI from baseline to 3 months between predictor groups were estimated. The treatment effects and corresponding P-values represent the comparison of exenatide vs. placebo within each sub-group (i.e. the placebo-subtracted treatment effect) (Figure 2). Interaction P-values are also shown. Each dot represents the mean percent BMI reduction at 3 months within each sub-group, along with 95% confidence intervals. As can be appreciated from Figure 2, the clearest separations for percent change in BMI are for gender and baseline appetite. While other factors will be investigated in our proposed trial, we will focus primarily on gender and appetite as predictors of weight loss response.

<u>Study #4: Short-Term Weight Loss with Meal Replacements in Adolescents with Severe Obesity</u>

The use of meal replacements (structured meals consisting of liquid shakes and frozen entrees of known caloric content) represents one promising treatment approach for obesity. A meta-analysis of studies among obese adults has shown that meal replacements reduce body weight to a greater extent than conventional dieting alone.[57] The rationale for the use of meal replacements is that individuals with obesity, including adolescents,[58] often under-estimate caloric intake and that adherence to a strict, pre-determined meal regimen removes the "guess-work" from eating. The use of meal replacements is relatively new in the context of pediatric obesity management but a recent study by Berkowitz et al.[55] demonstrated promising short-term weight loss efficacy (BMI reduction of approximately 6%) in adolescents with severe obesity using meal replacements for a period of 4 months. However, weight loss maintenance was hampered by poor long-term compliance and weight regain ensued.[55]

Figure 3. Trajectory of BMI Reduction with Short-Term Meal Replacements in Adolescents



We are currently conducting a clinical trial that includes a one-month meal replacement induction period and have observed promising BMI reduction among adolescents with severe obesity (N=17). Mean BMI reduction was 3.4% in only four weeks (Figure 3); participants in the proposed trial will have up to 12 weeks of meal replacements. Should this trajectory continue, we expect the majority would achieve ≥5% BMI reduction within 12 weeks. Therefore, based upon results from Berkowitz et al.[55] and our pilot data, we believe the proposed approach is feasible and the BMI goal is attainable.

In summary, our extensive portfolio of preliminary work: 1) demonstrates our group's leadership role in, and commitment to, the field of pediatric obesity medicine; 2) provides initial evidence regarding the safety and efficacy of GLP-1RA treatment in adolescents with severe obesity; 3) highlights the benefits (short-term weight loss) and limitations (long-term weight regain) of meal replacement therapy; and 4) sets the stage for taking the next important step toward developing comprehensive and appropriately-intensive treatment strategies for teens afflicted with severe obesity. The logical extension of our previous work is to evaluate the most promising aspect of meal replacement therapy (short-term weight loss) in combination with pharmacotherapy aimed at weight loss maintenance.

1.4 Dose Rationale and Risk/Benefits – Use in the Pediatric Population

We will utilize the once-weekly, extended-release formulation of exenatide, a long-acting GLP-1RA. The frequency and intensity of GI side effects, such as nausea and vomiting, are lower with long-acting GLP-1RA agents, which should be associated with better tolerability (a prime consideration in pediatric medicine). The newly-approved injection device for extended-release exenatide is easy-to-use and similar to the short-acting devices. Despite a lower incidence of nausea, weight reduction with extended-release exenatide is similar to the twice per day formulation.[59-62] Extended-release exenatide is administered one time per week by subcutaneous injection in the upper arm, abdomen, or thigh. Exenatide will be initiated and maintained at a dose of 2.0 mg per week. The 2.0 mg dose was shown to achieve plasma concentrations similar to the maximum concentration achieved with a single injection of 10 mcg exenatide and was demonstrated to be the most efficacious dose for weight loss.[62] Exenatide and matching placebo will be donated by Astra Zeneca Pharmaceuticals. Placebo/exenatide devices will be indistinguishable. Study drug and placebo will be managed by the University of Minnesota Investigational Drug Service Pharmacy. Education will be provided by a trained study coordinator and/or physician. Subjects will be instructed to administer the medication under the supervision of a parent/guardian, and will be required to complete a study medication log.

2 Study Objectives

2.1 Primary Objective

Evaluate the effect of GLP-1RA treatment on the maintenance of weight loss and durability of cardiometabolic risk factor improvements among adolescents with severe obesity following a meal replacement induction period. We hypothesize that adolescents with severe obesity receiving GLP-1RA treatment following a short-term meal replacement induction period will demonstrate superior maintenance of initial BMI reduction 52 weeks following randomization compared to those assigned to placebo (primary endpoint) and that a higher proportion of those assigned to GLP-1RA treatment vs. placebo will maintain ≥5% BMI reduction from baseline to the 52-week time point (secondary endpoint). Moreover, GLP-1RA treatment will result in superior maintenance of initial reductions of body fat (total, visceral, and subcutaneous), blood pressure, triglycerides/HDL ratio, inflammation, oxidative stress, postprandial glucose-insulin response, insulin resistance, and β cell dysfunction at 52 weeks.

2.2 Secondary Objectives

Investigate the mechanisms by which GLP-1RA treatment facilitates weight loss maintenance and identify predictors of response to treatment. We hypothesize that compared to placebo, GLP-1RA treatment following a period of meal replacement will reduce appetite (and related hormones) and gastric emptying rate, and will increase satiety (and related hormones) and resting energy expenditure at 26- and 52 weeks following randomization. Moreover, based on our preliminary work, we hypothesize that appetite (and appetite-related hormones) following the meal replacement period and female gender will be associated with superior weight loss maintenance with GLP-1RA treatment.

3 Study Design

3.1 General Design

This will be a randomized, double-blind, placebo-controlled clinical trial specifically designed to evaluate the effectiveness of GLP-1RA treatment to improve weight loss maintenance following a short-term (up to 8 weeks) meal replacement induction period among up to 100 adolescents with severe obesity. Because the trial is designed to evaluate weight loss maintenance, participants must achieve at least 5% BMI reduction during the meal replacement induction period in order to be randomized. Weight checks will be performed regularly (week 4 and 8 with an optional week 6 weight check) during the induction period, and randomization will occur as soon as the 5% BMI reduction benchmark has been achieved (i.e., it may not take the full 8 weeks for some participants to be randomized – it could occur at week 4, 6 or 8). Participants who do not achieve the 5% BMI reduction benchmark will not continue in the trial. However, these participants (i.e. those who experienced a reduction in BMI but did not quite achieve the 5% benchmark) will be given the option to undergo reassessment of some of the procedures performed at baseline to evaluate whether BMI reduction less than 5% can improve cardiometabolic risk factors. This will be considered an ancillary study and individuals who agree to participate, and their parents, will sign a separate assent and consent form, respectively. After achieving the 5% BMI reduction benchmark, participants will be randomized (1:1) to either exenatide or placebo for a subsequent period of 52 weeks. During the meal replacement induction period, all participants will engage in a meal replacement therapy protocol designed to achieve BMI reduction of at least 5% in a maximum timeframe of 8 weeks. We believe the goal of 5% BMI reduction over a period of 8 weeks is realistically achievable for most individuals based on the study by Berkowitz et al.[55] and on our unpublished data

demonstrating a mean BMI reduction of 3.4% with only 4 weeks of meal replacement therapy in 17 participants.

3.2 Primary and Secondary Study Endpoints

The primary analysis will compare the mean BMI percent change from randomization to 52 weeks of follow-up between GLP-1RA and placebo groups, adjusted for randomization values of BMI. Confidence intervals (CIs) and P-values will be based on robust variance estimation. Statistical significance will be considered as $p<0.05$. Adjustment for residual imbalances may be made between treatment groups after randomization (e.g., in sex). We will also evaluate differences in the proportion of subjects able to maintain ≥5% reduction from baseline with CIs and P-values based on the Chi-squared test.

Secondary endpoints of body fat (total body-, visceral-, and subcutaneous fat), triglycerides/HDL ratio, blood pressure, inflammation, oxidative stress, postprandial glucose and insulin response, insulin resistance, and beta cell dysfunction will be characterized over the full length of follow-up for each time point they are measured. The evaluation will be in a similar fashion as the primary outcome wherein analyses will be adjusted for randomization values. Longitudinal analyses will also be conducted, incorporating the multiple time points these features are measured.

Mechanism of action metrics of appetite and satiety at 52 weeks follow-up will each be evaluated in a similar fashion as other secondary endpoints wherein analyses will be adjusted for values at randomization and CIs and P-values will use robust variance estimation. Potential effect modifiers of appetite at randomization (high vs. low, based on CEBQ cutoff and area-under-the-curve for visual analog scale and meal test hormones) and gender will each be evaluated separately for estimates of treatment effect within each subgroup along with a test of interaction.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- BMI ≥1.2 times the 95th percentile (based on sex and age) or BMI ≥35 kg/m^2
- 12-17 years old

4.2 Exclusion Criteria

- Tanner stage <2
- Type 1 or 2 diabetes mellitus
- Previous (within 6 months) or current use of medication(s) prescribed primarily for weight loss (refer to appendix material for comprehensive list)
- If currently using weight altering drug(s) for non-obesity indication(s) (refer to appendix material for comprehensive list), any change in drug(s) or dose within the previous 6 months
- Previous bariatric surgery
- If currently using anti-hypertensive medication(s), lipid medication(s), and/or medication(s) to treat insulin resistance (refer to appendix material for comprehensive list), any change in drug(s) or dose within the previous 6 months
- If currently using CPAP/BIPAP (for sleep apnea), change in frequency of use or settings within the previous 6 months
- History of treatment with growth hormone

- Neurodevelopmental disorder severe enough to impair ability to comply with study protocol
- Clinical diagnosis of bipolar illness, schizophrenia, and/or conduct disorder
- Substance abuse
- Females: currently pregnant, planning to become pregnant, or unwilling to use 2 or more acceptable methods of contraception when engaging in sexual activity throughout the study
- Tobacco use
- Liver/renal dysfunction
- ALT or AST >2 times the upper limit of normal (Note: Non-alcoholic fatty liver disease is highly prevalent in the target population and is NOT an exclusionary criterion. Thus, if non-alcoholic fatty liver disease is suspected as the cause of elevated ALT or AST, it is at the discretion of the medical safety officer to order a liver ultrasound and relevant labs to rule out other potential causes of liver enzyme elevation. If other causes are ruled out based on results of the work up, participant may be enrolled in the trial, again at the discretion of the medical safety officer.)
- Bicarbonate <18 mmol/L
- Creatinine >1.2 mg/dL
- History of pancreatitis
- Personal- and/or family history of medullary thyroid carcinoma
- Personal- and/or family history of multiple endocrine neoplasia type 2
- Calcitonin level >50 ng/L
- Bulimia nervosa
- Neuromuscular disorder
- Hypothalamic obesity
- Obesity associated with genetic disorder (monogenetic obesity)
- Hyperthyroidism or uncontrolled hypothyroidism
- History of suicide attempt
- History of suicidal ideation or self-harm within the past year
- History of cholelithiasis

Patients will be recruited from the Pediatric Weight Management Clinic at the University of Minnesota Masonic Children's Hospital and referred from the MN-POC member institutions. Additional recruitment strategies may include advertisements, study-specific recruitment letters sent to potentially-eligible patients in the respective health systems of the MN-POC (Fairview for the University of Minnesota), and word of mouth. Appropriate designees will discuss study participation with interested participants and their parents at which time the initial consent and assent discussion will be conducted.

4.3 Early Withdrawal of Participants

4.3.1 When and How to Withdraw Participants

Participants may withdraw from the trial at any time. The study may also be stopped at any time by the principal investigator, medical officer, IRB, or the FDA for any reason. Participants who discontinue participation and withdraw consent/assent will not complete follow-up visits. However, participants who are not fully compliant with the medication regimen and/or who choose to stop the medication altogether but do not withdraw consent will remain in the study for follow-up in order to preserve the ability to perform

an ITT analysis. Upon completion of the trial or upon complete withdrawal from the trial, participants will be referred back to their primary care physician, if applicable.

4.3.2 Data Collection and Follow-up for Withdrawn Participants

If a participant withdraws consent to participate in the trial, attempts will be made to obtain permission to record follow-up data. Attempts to follow up will include three phone calls to the participant. A participant will be considered lost to follow-up if no response is obtained after three attempts.

5 Study Drug

5.1 Treatment Regimen

Following the meal replacement induction period, and if successful in achieving ≥5% BMI reduction, participants will be randomized (1:1) to either exenatide or placebo. Extended-release exenatide will be initiated and maintained at a dose of 2.0 mg per week.

5.2 Method for Assigning Subjects to Treatment Groups

Each participant will be randomly assigned (1:1) to active drug or placebo using permuted blocks of size 2, 4, or 6. For eligible participants who are randomized, a randomization number will be assigned starting with R001 and numbered sequentially. Randomization codes will be maintained at the University of Minnesota Investigational Drug Service Pharmacy. The medical officer and PI will be responsible for determining when individual treatment assignments should be un-blinded (e.g., safety issues).

5.3 Preparation and Administration of Study Drug

Study drug and placebo will be obtained, managed, dispensed, and tracked by the IDS pharmacy at the University of Minnesota.

5.4 Participant Compliance Monitoring

Study drug compliance will be assessed at all follow up visits. Participants will be given a medication journal in which they will be required to track when medication is administered as well as any symptoms experienced while taking the medication. Participants will be required to bring study medication/placebo to all visits for compliance assessment.

5.5 Prior and Concomitant Therapy

Concomitant medication(s) status will be collected at the baseline visit. Changes in concomitant medication(s) will be assessed during follow-up visits.

5.6 Packaging

Drug/placebo will be blinded and dispensed by the University of Minnesota IDS Pharmacy. Astra Zeneca Pharmaceuticals will send study supplies directly to the University of Minnesota IDS Pharmacy, which will be responsible for tracking and handling the material.

5.7 Receiving, Storage, Dispensing and Return

5.7.1 Receipt of Drug Supplies

Upon receipt of the study medication and supplies, an inventory will be performed and a drug receipt log completed and signed by IDS staff. IDS staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or

unusable study drug in a given shipment will be documented in the study files. IDS staff will notify the investigator of any damaged or unusable study drug. A chain of custody will be maintained by IDS staff.

5.7.2 Storage

Study medication will be stored in a temperature-controlled and locked room in IDS Pharmacy with minimum access and controlled environmental conditions.

5.7.3 Dispensing of Study Drug

Study drug/placebo will be dispensed from the IDS. Study drug reconciliation/chain of custody will be performed on a regular basis to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug dispensation case report form.

5.7.4 Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug consumed and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to the destruction of unused study drug. Drug destroyed on site will be documented in the study files and completed per the IDS standard operating procedures.

6 Study Procedures

Participants will be asked to administer trial medication/placebo but withhold all other concomitant medication(s), if applicable, for study visits. Table 3 shows the procedures to be performed and data to be collected at each study visit (please refer to the detailed breakdown of visits following the table for comprehensive list of assessments/procedures). All participants will receive reimbursement payments for completing study visit assessments. Note: 6- and 8-week meal replacement visits may be unnecessary for some participants (those who achieve 5% BMI reduction early) and the 6-week weight check visit is optional.

Table 3. Measured Variables by Visit

	Baseline	4 Weeks Meal Repl.	6 Weeks Meal Repl.	8 Weeks Meal Repl.	Randomization	4 Weeks	12 Weeks	26 Weeks	39 Weeks	52 Weeks
Physical Exam	X									
Tanner Staging	X				X			X		X
Safety Labs	X				X	X	X	X	X	X
ECG	X				X			X		X
Bone Age X-Ray	X				X					X
Fasting labs and blood biomarkers	X				X					X
BMI/anthropometrics	X	X	X	X	X	X	X	X	X	X
iDXA scan	X				X			X		X
Metabolic Rate	X				X			X		X
Blood Pressure	X				X	X	X	X	X	X
Questionnaires*	X				X			X		X
PHQ-2 questionnaire	X	X	X	X	X	X	X	X	X	X
Meal Test	X				X			X		X
AE assessment		X	X	X	X	X	X	X	X	X
Compliance assessment		X	X	X	X	X	X	X	X	X
Lifestyle Counseling	X	X	X	X	X	X	X	X	X	X

* Questionnaires include PedsQL (Young Adult Quality of Life Inventory), Child and Parent Questionnaire, PEDSQL Gastrointestinal Symptoms Scale, Impact of Weight on Quality of Life (IWQOL-KIDS), Children's Power of Food Scale, Adult Eating Behavior Questionnaire (AEBQ), Dutch Eating Behavior Questionnaire, Questionnaire of Eating and Weight Patterns-Adolescent (QWEP), Depression Scale for Children (CES-DC), Screen for Child Anxiety Related Disorders (SCARED), Physical activity patterns questionnaire, and (if applicable), questionnaires examining dietary habits, quality of life and physical activity patterns

6.1 Screening Visit or Phone Call

- Informed consent/assent
- Medical record review
- Evaluation against inclusion and exclusion criteria
- Remind participant to fast for 8 hours prior to baseline visit

6.2 Baseline Visit

(Visit completed following an 8-hour fast and confirmation that all medications have been withheld on the morning of the study visit)
Screening and baseline visit may be completed on the same visit day.

- Informed consent/assent, if not previously obtained
- Interim medical history review (if screening visit occurred previously)
- Vital signs (heart rate and blood pressure)
- Concomitant medications
- Anthropometric measurements (height, weight, hip/waist circumference, body mass index, iDXA)
- Physical exam with Tanner (pubertal) stage determination (note: if Tanner 5, exam does not need to be repeated at subsequent visits)
- Urine pregnancy test for all female subjects
- Questionnaires:
  - PedsQL™ (Young Adult Quality of Life Inventory) Child and Parent Questionnaire
  - PedsQL™ Gastrointestinal Symptoms Scale
  - Impact of Weight on Quality of Life: IWQOL-Kids
  - Children's Power of Food Scale

    - Adult Eating Behavior Questionnaire (AEBQ)
    - Dutch Eating Behavior Questionnaire
    - Questionnaire of Eating and Weight Patterns-Adolescent (QEWP)
    - Depression Scale for Children (CES-DC)
    - Screen for Child Anxiety Related Disorders (SCARED)
    - Physical activity patterns questionnaire
    - PHQ-2
    - If applicable, additional questionnaires examining dietary habits, quality of life, and physical activity patterns
- Fasting blood draw: complete metabolic panel, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), insulin, hemoglobin A1c, calcitonin, amylase, lipase, prolactin, TSH, FSH, LH, testosterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), and carcinoembryonic antigen (CEA) – Note: the safety labs drawn at this visit will serve as the screening labs for trial eligibility and qualification to receive study drug/placebo
- ECG
- Bone age x-ray
- Blood draw for frozen plasma and serum storage
- Resting metabolic rate assessment
- Meal test
- Urine sample collection for frozen storage
- Meal replacement instructions (including food journaling to track compliance)
- Lifestyle/behavioral modification counseling
- For all female subjects, contraceptive counseling and confirmation of use of 2 acceptable forms of contraception when engaging in sexual activity throughout the study (acceptable methods are described in the counseling tool document, which will be given to subjects and discussed at each visit and phone call)
- Dispensation of meal replacement shakes and entrees (or order placement for home delivery)

6.3 4-Week, 6-Week (optional), and 8-Week Meal Replacement Phase Visits

(note: 6- and 8-week visits may be unnecessary if 5% BMI reduction is achieved at previous visit)

6 week (optional), and 8 weeks ± 3 days from baseline visit

- Anthropometric measurements (height, weight, hip/waist circumference, body mass index)
- Adverse event assessment
- Meal replacement compliance assessment
- Lifestyle/behavioral modification counseling
- Dispensation of meal replacement shakes and entrees (or order placement for home delivery)
- PHQ-2

6.4 Randomization Visit – Study Medication Phase

(note: the randomization visit will occur in place of the 4-week, 6-week, or 8-week visit, shown above, if 5% BMI reduction is achieved at that time-point)

(Visit completed following a 8-hour fast and confirmation that all medications have been withheld on the morning of the study visit)
Refer to visit windows at 4-, 6-, and 8-weeks above

- Interim medical history review
- Vital signs (heart rate and blood pressure)
- Review concomitant medications
- Anthropometric measurements (height, weight, hip/waist circumference, body mass index, iDXA)
- Tanner stage determination
- Urine pregnancy test for all female subjects
- PHQ-2
- Questionnaires:
  - PedsQL™ (Young Adult Quality of Life Inventory) Child and Parent Questionnaire
  - PedsQL™ Gastrointestinal Symptoms Scale
  - Impact of Weight on Quality of Life: IWQOL-Kids
  - Children's Power of Food Scale
  - Adult Eating Behavior Questionnaire (AEBQ)
  - Dutch Eating Behavior Questionnaire
  - Questionnaire of Eating and Weight Patterns-Adolescent (QEWP)
  - Depression Scale for Children (CES-DC)
  - Screen for Child Anxiety Related Disorders (SCARED)
  - Physical activity patterns questionnaire
  - If applicable, additional questionnaires examining dietary habits, quality of life, and physical activity patterns
- Fasting blood draw: complete metabolic panel, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), insulin, hemoglobin A1c, calcitonin, amylase, lipase, prolactin, TSH, FSH, LH,

testosterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), and carcinoembryonic antigen (CEA)
- ECG
- Blood draw for frozen plasma and serum storage
- Resting metabolic rate assessment
- Meal test
- Urine sample collection for frozen storage
- Lifestyle/behavioral modification counseling
- For all female subjects, contraceptive counseling and confirmation of use of 2 acceptable forms of contraception when engaging in sexual activity throughout the study (acceptable methods are described in the counseling tool document, which will be given to subjects and discussed at each visit and phone call)
- Randomization to study medication or placebo
- Study medication/placebo administration and dose escalation training
- Dispensation of study medication/placebo

6.5 4-Week Follow-up Visit

4 weeks ± 3 days from randomization visit

- Interim current health/medical history review
- Review concomitant medications
- Blood draw for safety labs: complete metabolic panel, and calcitonin
- Adverse event assessment
- Assessment of injection site reactions (incidence and severity)
- Study drug/placebo compliance/accountability
- Anthropometrics (height, weight, hip/waist circumference, body mass index)
- Vital signs (heart rate and blood pressure)
- Lifestyle/behavioral modification counseling
- Urine pregnancy test for all female subjects; for all female subjects, contraceptive counseling, confirmation of use of 2 acceptable forms of contraception when engaging in sexual activity, and dispensation of home pregnancy tests (all female patients will be instructed to perform test monthly and contact study staff immediately if positive)
- Dispensation of study medication/placebo
- PHQ-2

6.6 12-Week Follow-up Visit

12 weeks ± 7 days from randomization visit

- Interim current health/medical history review
- Review concomitant medications
- Blood draw for safety labs: complete metabolic panel, and calcitonin
- Adverse event assessment
- Assessment of injection site reactions (incidence and severity)
- Study drug/placebo compliance/accountability
- Anthropometrics (height, weight, hip/waist circumference, body mass index)
- Vital signs (heart rate and blood pressure)

- Lifestyle/behavioral modification counseling
- Urine pregnancy test for all female subjects; for all female subjects, contraceptive counseling, confirmation of use of 2 acceptable forms of contraception when engaging in sexual activity, and dispensation of home pregnancy tests (all female patients will be instructed to perform test monthly and contact study staff immediately if positive)
- Dispensation of study medication/placebo
- PHQ-2

6.7 26-Week Follow-up Visit

(Visit completed following a 8-hour fast and confirmation that all medications, except study medication/placebo, have been withheld on the morning of the study visit)
26 weeks ± 7 days from randomization visit

- Interim medical history review
- Vital signs (heart rate and blood pressure)
- Review concomitant medications
- Adverse event assessment
- Assessment of injection site reactions (incidence and severity)
- Study drug/placebo compliance/accountability
- Anthropometric measurements (height, weight, hip/waist circumference, body mass index, iDXA)
- Tanner stage determination
- Urine pregnancy test for all female subjects
- PHQ-2
- Questionnaires:
  - PedsQL™ (Young Adult Quality of Life Inventory) Child and Parent Questionnaire
  - PedsQL™ Gastrointestinal Symptoms Scale
  - Impact of Weight on Quality of Life: IWQOL-Kids
  - Children's Power of Food Scale
  - Adult Eating Behavior Questionnaire (AEBQ)
  - Dutch Eating Behavior Questionnaire
  - Questionnaire of Eating and Weight Patterns-Adolescent (QEWP)
  - Depression Scale for Children (CES-DC)
  - Screen for Child Anxiety Related Disorders (SCARED)
  - Physical activity patterns questionnaire
  - If applicable, additional questionnaires examining dietary habits, quality of life, and physical activity patterns
- Fasting blood draw: complete metabolic panel, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), insulin, hemoglobin A1c, calcitonin, amylase, lipase, prolactin, TSH, FSH, LH, testosterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), and carcinoembryonic antigen (CEA)
- ECG
- Blood draw for frozen plasma and serum storage
- Resting metabolic rate assessment
- Meal test
- Urine sample collection for frozen storage

- Lifestyle/behavioral modification counseling
- For all female subjects, contraceptive counseling and confirmation of use of 2 acceptable forms of contraception when engaging in sexual activity throughout the study (acceptable methods are described in the counseling tool document, which will be given to subjects and discussed at each visit and phone call)
- Dispensation of study medication/placebo

6.8 39-Week Follow-up Visit

39 weeks ± 7 days from randomization visit

- Interim current health/medical history review
- Review concomitant medications
- Blood draw for safety labs: complete metabolic panel, and calcitonin
- Adverse event assessment
- Assessment of injection site reactions (incidence and severity)
- Study drug/placebo compliance/accountability
- Anthropometrics (height, weight, hip/waist circumference, body mass index)
- Vital signs (heart rate and blood pressure)
- Lifestyle/behavioral modification counseling
- PHQ-2
- Urine pregnancy test for all female subjects; for all female subjects, contraceptive counseling, confirmation of use of 2 acceptable forms of contraception when engaging in sexual activity, and dispensation of home pregnancy tests (all female patients will be instructed to perform test monthly and contact study staff immediately if positive)
- Dispensation of study medication/placebo

6.9 52-Week Follow-up Visit

(Visit completed following a 8-hour fast and confirmation that all medications, except study medication/placebo, have been withheld on the morning of the study visit)
52 weeks ± 7 days from randomization visit

- Interim medical history review
- Vital signs (heart rate and blood pressure)
- Review concomitant medications
- Adverse event assessment
- Assessment of injection site reactions (incidence and severity)
- Study drug/placebo compliance/accountability
- Anthropometric measurements (height, weight, hip/waist circumference, body mass index, iDXA)
- Tanner stage determination
- Urine pregnancy test for all female subjects
- PHQ-2
- Questionnaires:
  - PedsQL™ (Young Adult Quality of Life Inventory) Child and Parent Questionnaire
  - PedsQL™ Gastrointestinal Symptoms Scale
  - Impact of Weight on Quality of Life: IWQOL-Kids

- Children's Power of Food Scale
- Adult Eating Behavior Questionnaire (AEBQ)
- Dutch Eating Behavior Questionnaire
- Questionnaire of Eating and Weight Patterns-Adolescent (QEWP)
- Depression Scale for Children (CES-DC)
- Screen for Child Anxiety Related Disorders (SCARED)
- Physical activity patterns questionnaire
- If applicable, additional questionnaires examining dietary habits, quality of life, and physical activity patterns

- Fasting blood draw: complete metabolic panel, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), insulin, hemoglobin A1c, calcitonin, amylase, lipase, prolactin, TSH, FSH, LH, testosterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), and carcinoembryonic antigen (CEA)
- ECG
- Bone age x-ray
- Blood draw for frozen plasma and serum storage
- Resting metabolic rate assessment
- Meal test
- Urine sample collection for frozen storage
- For all female subjects, contraceptive counseling and confirmation of use of 2 acceptable forms of contraception when engaging in sexual activity throughout the study (acceptable methods are described in the counseling tool document, which will be given to subjects and discussed at each visit and phone call)

6.10 Phone Call/Email/Text message – Weeks 8, 16, 20, 30, 34, 43, and 47

± 7 days from randomization

- Interim current health/medical history review including changes to concomitant medications
- Adverse event assessment
- Study drug/placebo compliance/accountability
- For all female subjects, contraceptive counseling and confirmation of use of 2 acceptable forms of contraception when engaging in sexual activity
- Lifestyle/behavioral modification counseling

6.11 Detailed Study Procedures

6.11.1 Anthropometric Measurements and Assessment of Pubertal Status

Height and weight will be measured using a calibrated, wall-mounted stadiometer and an electronic scale, respectively. Measurements will be obtained with participants in light clothing, without shoes. Two consecutive height and weight measurements will be obtained and averaged. If the first two values differ by more than 0.5 cm for height and/or 0.3 kg for weight, a third measurement will be obtained and the average of three measurements will be calculated. BMI will be calculated as the weight in kilograms divided by the height in meters, squared. Waist circumference will be measured at end-expiration midway between the base of the rib cage and the superior iliac crest. Hip circumference will be measured at the maximal protuberance of the buttocks. Two

consecutive waist and hip measurements will be averaged. If the first two values for either measure differ by more than 0.3 cm, a third measurement will be obtained and the average of three measurements will be calculated. Total percent body fat, visceral fat (novel feature of the iDXA), and lean muscle mass will be determined by dual energy x-ray absorptiometry (iDXA, GE Healthcare). The scanning table accommodates body sizes of up to 204 kg. Tanner stage will be determined by a trained pediatrician or a trained nurse.

6.11.2 Blood Pressure and Heart Rate

Blood pressure measurements will be obtained manually on the same arm using the same cuff size and equipment. Standardized procedures will be employed as described in previously published standards.[63] Individual cuff size will be determined by measuring the arm circumference midway between the acromial process and the bony olecranon. Sitting blood pressure and heart rate will be measured after the participant has been resting quietly without legs crossed for 10 minutes. Measurements will be made three consecutive times (3-minute intervals). The final two of three independent measurements will be averaged.

6.11.3 Blood Analyses

Fasting (≥8 hours) blood will be collected for the measurement of lipids (total-, LDL-, HDL-cholesterol, and triglycerides), glucose, insulin, and hemoglobin A1c (to be assayed in Fairview Diagnostics Laboratories, Fairview-University Medical Center, Minneapolis, MN - a Center for Disease Control and Prevention certified laboratory). Fasting samples for C-reactive protein and oxidized LDL cholesterol, along with the biomarkers obtained from the standardized meal tests, will be processed and stored at -80 degrees C for a batched analysis in the University of Minnesota Cytokine Reference Laboratory (CLIA licensed).

6.11.4 Lifestyle/Behavioral Modification Counseling

All participants, regardless of group assignment, will receive the same lifestyle/behavioral modification counseling monthly throughout the entire study: delivered at each in-person study visit and on the phone for months when there is no study visit. The lifestyle/behavioral modification curriculum has been adapted from the NIDDK-sponsored TODAY study lifestyle modification program materials[64] and utilized by our group in a previous[54] and ongoing trial. Trained study coordinators will deliver the lifestyle/behavioral modification counseling, which will focus on small, successive changes in dietary (after meal replacement induction period) and physical activity behaviors through the use of evidence-based behavior change strategies such as self-monitoring, goal setting, reinforcement for goal achievement, stimulus control, social support, problem solving, and motivational techniques. The educational materials will be given to subjects and parents at the first study visit and selected sections will be reviewed and discussed at each face-to-face and phone-based lifestyle modification counseling session. We have previously demonstrated the effectiveness of this lifestyle modification protocol in a randomized, placebo-controlled trial among adolescents with severe obesity.[54] The intensity of the lifestyle modification is designed to be practical and feasible in the clinic setting.

6.11.5 Meal Replacement Induction Period

All participants will engage in a meal replacement induction period (that will range from 4 to 8 weeks) with a goal of reducing individual BMI by at least 5%. The meal replacement plan has been used successfully in adolescents with severe obesity.[55] Participants will be asked to strictly follow the prescribed eating regimen, which will include three Slim-Fast® shakes (one for breakfast and two for lunch or vice-versa), two pre-packaged frozen entrée meals for dinner (Weight Watchers, Smart Ones®), two servings of fruit, and three servings of vegetables per day (Note: shakes contain 190 kcals each (570 total) + meals contain 250 kcals each (500 total) + fruits and vegetables will provide approximately 300 total kcals = 1370 total kcals per day). Shakes/meals will be provided free of charge – fruits/vegetables will be purchased by the participants. Guidance will be provided regarding the use of the meal replacement shakes at school, and participants will be encouraged to engage in family meal sessions despite eating different foods. Meal replacement compliance will be assessed by requiring participants to maintain a dietary log throughout the trial. The percentage of days for which the protocol was strictly followed (no additional calories consumed) will serve as the primary metric of compliance. Study coordinators will perform weekly reminder phone calls during which the importance of maintaining the dietary log will be emphasized.

6.11.6 Questionnaires

Self-report appetite and satiety will be measured using the AEBQ. Additional relevant eating behavior domains addressed in the AEBQ include emotional overeating and enjoyment of food (hedonic eating). Additional questionnaires will address disordered eating patterns, anxiety, depression, etc. These questionnaires, and others that might be added, will allow us to examine the impact of other eating behaviors and external factors in relation to weight loss. However, results will be considered hypothesis-generating.

An individual who receives a score of 3 or greater on the PHQ-2 will be referred to the study psychometrist, Amy Gross, for a follow-up clinical interview. Dr. Gross and Dr. Fox will then make a determination about whether or not the participant can remain in the trial or should be withdrawn.

6.11.7 Standardized Meal Test

The standardized meal test will serve many purposes in this study and will be performed at baseline, randomization, 26- and 52 weeks. After having fasted for ≥8 hours, participants will consume (within five minutes) a fixed-size, single-item breakfast meal of chilled Optifast (474 mL, 320 kcals, 50% carbohydrate, 35% protein, 15% fat; Novartis). Fasting (-10 minutes and 0 minutes) and serial postprandial (15-, 30-, 45-, 60-, and 90-, and 120-minutes: 8 total blood sampling time-points) plasma concentrations of glucose, insulin, C-peptide and a panel of hormones either directly or indirectly associated with appetite, satiety, and/or energy intake including leptin, ghrelin, peptide YY (PYY), GLP-1, glucose-dependent insulinotropic polypeptide (GIP), amylin, pancreatic polypeptide, and cholecystokinin will be measured (will require insertion of a polyethylene catheter in an antecubital vein), along with ratings on 15-cm visual analog scales from “not at all” to “extremely” for appetite, satiety, desire to eat, and nausea. This method has been validated for use in appetite research[69] and was recently utilized by Sysko et al.[70] in a study of adolescents with severe obesity. We will calculate the area-under-the-curve (AUC) for all the biomarkers and visual analog scale results for the entire standardize meal test. As recently reported,[71] the standardized meal test can be utilized to evaluate

insulin sensitivity and beta cell function. Gastric emptying rate will be measured during the meal test by obtaining serial samples (same time points as hormone measurements) of blood paracetamol (acetaminophen) levels (1,000 mg administered with the meal test, as previously described).[72]

6.11.8 Measurement of Energy Expenditure

Resting energy expenditure will be measured by indirect calorimetry after participants have been fasting for ≥8 hours. Metabolic data will be collected using a ventilated hood (Parvo Medics; Sandy UT). Previous investigations have shown the ventilated hood method to be more accurate and reliable when compared to the other techniques.[73, 74] This method has been shown to be more comfortable in tests that last more than five to ten minutes.[74] Participants will be instructed to not engage in exercise on the day prior to testing. Participants will be positioned comfortably in a semi-recumbent fashion for 60 minutes. Resting gas exchange measurements will be collected using a Parvo Medics TrueOne 2400 Metabolic Cart, (Sandy, UT). The cart will be calibrated for gas analyses and volume at least twice prior to each test session. Room air (25°C) will be drawn through the hood at a rate of 40 L/min. Resting metabolic rates will be collected over the initial 30-minute reclining period with the last 10-minutes averaged into an estimate of resting metabolic rate.

7 Statistical Plan

7.1 Participant Populations for Analysis

- Intent-to-treat (ITT): All participants randomized according to the treatment assignment received.
- Per-Protocol (PP): All participants randomized without protocol violations and who were compliant (at least 80% of planned doses) with the treatment assignment received. Protocol violations include: change in status of weight loss/altering medication(s).
- Safety Population: All participants who receive any amount of treatment according to the treatment they receive.

7.2 Sample Size Determination

Based on our preliminary data, results of the Berkowitz et al. trial,[55] and results of the Wadden et al. trial (in which 90% achieved 5% weight loss during the low calorie diet induction period),[34] we conservatively anticipate that at least 60% will achieve the 5% BMI reduction goal during the meal replacement induction period and would therefore be randomized. Considering a conservative dropout rate as high as 20% (our previous clinical trial experience with this population has been 10-15%),[50, 54] we will enroll 100 participants to have complete follow-up data at 52 weeks on at least 48 individuals. Table 4 presents the power associated with a placebo-subtracted BMI reduction ranging from 5-7% based on an overall sample size of 60 (30 in each treatment arm), variability estimates from the pilot trials[50, 54] suggesting a conservative standard deviation of approximately 6, and a conservative correlation between baseline and follow-up scores of 0.5.

Table 4. Power for Values of BMI Percent Change Treatment Effects at 52 weeks

Difference in BMI Percent Change	5%	6%	7%
Two-sided (N=60)	96.1%	99.4%	99.9%
Two-sided with 20% attrition (N=48)	91.5%	97.9%	99.7%

7.3 Statistical Methods

Descriptive analyses of baseline characteristics and outcomes will include means and standard deviations for continuous variables and frequencies for categorical variables. Treatment compliance will also be evaluated.

7.3.1 Primary Endpoint

The primary analysis will be conducted using the ITT population to compare the mean BMI percent change from randomization to 52 weeks of follow-up between GLP-1RA and placebo groups, adjusted for values of BMI at randomization for added precision. Confidence intervals (CIs) and P-values will be based on robust variance estimation. Statistical significance will be considered as $p<0.05$. Supportive analyses using the PP population will also be conducted along with consideration of adjustment for residual imbalances between treatment groups after randomization (e.g., in sex if there is a concerning imbalance between treatment arms). These results will be complemented with analyses summarizing the difference between treatment groups in the proportion of subjects able to maintain ≥5% reduction from baseline. Analyses will be summarized by an odds ratio through use of a logit link function and adjusted for BMI at randomization with robust variance estimates for confidence intervals and P-values.

7.3.2 Secondary Endpoints

Secondary endpoints of body fat (total body-, visceral-, and subcutaneous fat), triglycerides/HDL ratio, blood pressure, inflammation, oxidative stress, postprandial glucose and insulin response, insulin resistance, and beta cell dysfunction will be characterized over the full length of follow-up for each time point they are measured. The evaluation will be in a similar fashion as the primary outcome wherein analyses will be adjusted for values at randomization and robust variance estimation will be used for confidence intervals and P-values. Longitudinal analyses will also be conducted, incorporating the multiple time points at which these features are measured. Supportive analyses using the PP population will also be conducted.

Mechanism of action metrics of appetite and satiety at 52 weeks follow-up will each be evaluated in a similar fashion as other secondary endpoints wherein analyses will be adjusted for values at randomization and confidence intervals and P-values will use robust variance estimation.

7.3.3 Safety Analyses

The safety profile will be evaluated using the Safety analysis population and evaluated using data collected throughout follow-up. Analyses will be primarily descriptive reporting the number and percentage of adverse events along with categorizations of seriousness, severity, frequency (within a subject), and perceived relatedness to the intervention. In addition, safety labs of calcitonin, ALT, AST, amylase, lipase, prolactin, TSH, FSH, LH, testosterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), carcinoembryonic antigen (CEA), and creatinine, along with change in sexual maturation, bone mineral content from iDXA scans, bone age, QTc interval from ECG, injection site reactions, and gastrointestinal side effects will be evaluated between groups and monitored by the data and safety monitoring board (DSMB) throughout the trial.

7.3.4 Exploratory Analyses

Exploratory analyses will include investigating potential treatment effect modifiers of appetite at randomization (high vs. low, based on AEBQ cutoff and alternatively area-under-the-curve from the visual analog scale and meal test hormones) and sex. These will each be evaluated separately for estimates of treatment effect within each subgroup along with a test of interaction analyzed in a similar fashion as the primary endpoint, with adjustment for BMI values at randomization. Complementary analyses using the PP population will also be conducted.

7.4 Missing Data

Despite best efforts to avoid missing data, it is possible that some data will be missing, which could limit the interpretation and generalizability of results. If the missing data is missing completely at random, the consequence will merely be lost precision. Based upon attrition rates in our previous trials,[50, 54] we conservatively anticipate that no more than 20% of the subjects will be lost to follow-up. Taking this into account, the planned enrollment of 100 is inflated to account for potential drop out. As such, in the 'worst case' situation of randomizing only 60 participants and observing missing data as high as 20%, we will still have >90% power to detect a 5% placebo-subtracted change in BMI from randomization to 52 weeks (primary endpoint). If the data are missing at random, conditioned on measured covariates, then supplementary analyses adjusting for these covariates will produce unbiased results. For potential missing data mechanisms beyond measured covariates, we will examine the extent to which results may be affected through sensitivity analyses.

Imputation techniques will be considered for missing data issues, e.g., multiple imputation. In particular, in the event there is missing data for the primary analysis, we will use a last observation carried forward approach. Sensitivity analyses will also be conducted, using multiple imputation. Variables to be included in the imputation analysis model include sex, and age along with baseline and interim visit values. In this fashion, observations obtained during interim visits will be used to facilitate these analyses. Analyses will be based on 100 imputed values using Markov chain Monte Carlo simulation. Secondary endpoints will be handled similarly.

8 Safety and Adverse Events

8.1 Potential Risks

As with any research study, there may be unforeseen risks. A trained interdisciplinary research staff comprised of physicians, scientists, nurses, and coordinators carefully guard against all potential risks.

8.1.1 Dual-energy X-ray Absorptiometry (iDXA) Scan

The iDXA is painless and involves exposure to a very low dose of radiation. As part of this study, subjects will undergo a total of four iDXA scans.

8.1.2 Blood Sampling

There is minimal risk of bruising and infection associated with the blood draw.

8.1.3 Medication

All participants will be directed to immediately contact study staff if any symptoms of an adverse event are experienced regardless if the participant believes it may or may not be related to study medication.

Adverse events will be reviewed and documented at each study visit and phone call (monitored monthly throughout the study). Participants will be instructed to contact study staff immediately if any adverse event is experienced. Overall, the safety profile of exenatide is favorable, with nausea as the most commonly- reported side effect. The metabolic effects of exenatide are glucose-dependent; therefore, the risk of hypoglycemia is extremely low when used as a mono-therapy, as will be the case in the proposed study.[75] Mild injection site reactions (bruising, injection site pain, etc.) have ranged from 2-8% in studies with exenatide extended-release.[59-62] Evidence is mixed regarding whether acute pancreatitis and other potential pancreatic issues are associated with the use of GLP-1RAs among adult patients with T2DM. Although multiple studies have reported no association between GLP-1RA use and pancreatitis,[76-79] others have suggested a link.[80, 81] It is important to note that in the studies showing an association,[80, 81] the absolute increase in risk of pancreatitis was extremely low. In the proposed study, we will minimize any potential risk of pancreatitis by excluding patients with T2DM, a disease known to be associated with an increased risk of pancreatitis.[77] Furthermore, we will carefully monitor for reports of abdominal pain at each visit, and will measure lipase levels (pancreatic enzyme). Of note, the FDA and European Medicines Agency released communications in the summer of 2013 stating that available data do not confirm recent concerns over an increased risk for pancreatic side effects with GLP-1 based therapies.

8.1.4 Questionnaires

There are no risks associated with the questionnaires to be used in the study. Participants may refuse to answer any questions or stop participating at any time.

8.2 Definitions

8.2.1 Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or

worsens in severity during the course of the study. Inter-current illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Adverse events relationship to the study will be based on the following scale:

- Unrelated: Clearly not related to study
- Unlikely: Unlikely to be related to study
- Possible: May be related to study
- Probable: Likely to be related to study
- Definite: Clearly related to study

8.2.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the participant, and may require intervention to prevent one of the other serious outcomes noted above.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

8.2.3 Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment at which time a final phone call visit will be completed.

8.2.4 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will only be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.2.5 General Physical Examination Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities

that meet the definition of an adverse event will be recorded and documented as an adverse event.

8.2.6 Post-study Adverse Event

All unresolved adverse events will be followed until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the final visit, the participant and the parent/guardian will be instructed to report any subsequent event(s) that they, or their personal physician, believe might reasonably related to participation in this study.

8.2.7 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

8.2.8 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery will be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.3 Recording of Adverse Events

At each contact with the participant and their parent/guardian adverse events will be assessed by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event form. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, although they should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still

ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.4 Reporting of Serious Adverse Events

8.4.1 IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) will be submitted to the IRB within 10 working days if it falls under the UPIRTSO guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.4.2 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made

8.5 Un-blinding Procedures

When necessary, and at the discretion of the medical officer in consultation with the principal investigator, un-blinding on an individual-participant basis (e.g., adverse event related) will be performed by the University of Minnesota IDS Pharmacy.

8.6 Stopping Rules

In the event that a participant has a serious adverse event that is deemed study-related by the medical officer, the participant will be required to immediately discontinue the study drug. The overall study may be stopped at any time at the request of the DSMB, principal investigator, and/or medical officer. The main adverse effect that we expect to observe with GLP-1 treatment is gastrointestinal discomfort. In particular, nausea is a common side effect associated with treatment, especially within the first few weeks of initiation. Because this is an expected side effect and in many cases can be tolerated, participants who experience this adverse effect will not automatically be removed from the study. Participants will be removed from the study if gastrointestinal distress is deemed severe by the medical officer or if the participant is hospitalized for gastrointestinal-related symptoms. If more than five participants are hospitalized for gastrointestinal-related symptoms, the trial will be stopped. Participants will be instructed that they may withdraw from the study at any time and for any reason.

8.7 Medical Monitoring

Safety monitoring will include individual participant comprehensive assessment and appropriate reporting of adverse events as they occur. Adverse events will be monitored closely and participants will be provided with information about the risks/side effects of the study medication and provided with phone numbers to reach the principal investigator/study coordinator in case of emergencies.

8.8 Data and Safety Monitoring Board

A DSMB will be established, which will include at least one adult endocrinologist, one pediatric endocrinologist, and one biostatistician. DSMB members will not be affiliated with the study. The DSMB will meet regularly (frequency to be determined by DSMB members) during the trial to review data and evaluate participant safety. A charter for the DSMB to outline the responsibilities and procedures for the conduct of the monitoring board will be developed and approved by its members along with a plan for frequency of data review prior to the commencement of the trial. Review materials for the DSMB will be prepared and presented by the study biostatistician. A report from each meeting will be sent to the principal investigator and co-investigators advising on the continuation of the study.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents and Case Report Forms

All data will be collected and transcribed onto source documents. These source documents will act as the CRF. The source documents will have a unique identification number assigned by the study staff and will not include any personal identifiers.

9.3 Records Retention

The investigator will retain study essential documents for at least 6 years after the conclusion of the study.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The study will undergo regular monitoring (annually during the enrollment and follow up period) of the facility, staff, and study documents by clinical research associates in the University of Minnesota Clinical Trials Monitoring Service, which specializes in regulatory compliance for clinical trials associated with the Food and Drug Administration. This service provides regular monitoring of all research-related activities and is offered free of charge through the University of Minnesota CTSI. Monitoring staff will present a summary report to the PI after each site visit.

If necessary, corrective action plans will be devised and implemented by the PI to address deficiencies.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

11 Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

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

All participants and parents/guardians for this study will be provided an assent and consent form, respectively, describing this study and providing sufficient information for participants/families to make an informed decision about participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal assent of a participant and consent of the parent/guardian, using the IRB-approved assent and consent forms, must be obtained before that subject is submitted to any study procedure. This consent form will be signed by the participant or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Based upon guidance provided in 45 CFR 46, subpart D sections 401-409 regarding research in children, we believe that the proposed study poses greater than minimal risk but provides the prospect of direct benefit to the participants (half of the participants will be treated with GLP-1RA, which may provide benefit). The risk lies mainly in the administration of a medication approved for use in adults with type 2 diabetes in an “off label” population (adolescents ages 12-17) for an “off label” purpose (reduction of BMI and improvement of cardiometabolic risk factors and comorbidities). An Investigational New Drug (IND) exemption inquiry will be submitted (or a full IND application, if necessary) prior to commencement of the study (note: we received IND exemptions for our previous clinical trials with exenatide in the same patient population). We will utilize the expertise of staff in the IND Assistance Program, within the University of Minnesota Clinical and Translational Science Institute, to draft the IND exemption request/IND application.

Claudia Fox, M.D., M.P.H., a pediatrician who is board-certified in obesity medicine, will serve as the medical officer for the trial. The study will undergo regular monitoring by clinical research associates employed by the University of Minnesota Clinical Trials Monitoring Service, which specializes in regulatory issues related to studies monitored by the Food and Drug Administration. The following sections detail how each subpart D criterion will be satisfied: a) the risk is justified by the anticipated benefits to subjects; b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternate

approaches; and c) adequate provisions are made for soliciting the assent of the adolescents and permission of their parents or guardians.

11.1 Human Subjects Involvement and Characteristics

One-hundred (100) adolescents (ages 12-17 years old) with severe obesity (BMI ≥ 1.2 times the 95th percentile or BMI ≥35 kg/m^2) will be recruited from the University of Minnesota Children's Hospital, Pediatric Weight Management Clinic and member sites of the MN-POC: Mayo Clinic, Children's Hospitals and Clinics of Minnesota, and Park Nicollet. Adolescents are typically referred to these clinics to address issues related to excess body weight, comorbid conditions, and adverse cardiometabolic risk factors. Participants in this study will undergo a series of measurements of BMI, body composition, meal testing, and cardiometabolic risk factors, which will require blood draws. All costs of testing will be covered by the research study and subjects will be reimbursed for study participation.

11.2 Source of Research Materials

The following types of research material will be obtained from the participants: blood specimens, anthropometric data, blood pressure data, and other clinical variables. This material will be used exclusively for research. Pre-existing chart information will be used. Data obtained will be stored in a confidential database without direct subject identifiers. The principal investigator and designated study staff will have access to the subject linkages, which will be stored in a separate, secured location. Hard copies of data, including source documents with patient identifiers, will be kept in locked file cabinets in a locked office until the completion and publication of the study, at which point any patient identifiers will be removed and data will be stored at a secure storage facility for 6 years. Access to the locked file cabinet will be given to the study coordinators and principal investigator only. Any study files that will be shared with the University of Minnesota will remove patient identifying information.

11.3 Recruitment and Informed Consent

Subjects will be recruited from the University of Minnesota Masonic Children's Hospital, Pediatric Weight Management Clinic and member sites of the MN-POC. Appropriate designees will discuss study participation with interested participants and their parents at which time the initial consent and assent discussion will be conducted. Assent and consent will be obtained by the study coordinator after explaining the entire study in detail, asking the participant and the parent(s)/guardian(s) to explain the purpose, risk and benefits, and other details of the study, and giving the participant and parent(s)/guardian(s) an opportunity to ask questions. A copy of the assent and consent form will be given to the participants and parent(s)/guardian(s).

11.4 Potential Risks to Subjects

As with any research study, there may be unforeseen risks. A trained interdisciplinary research staff comprised of physicians, scientists, nurses, and study coordinators carefully guard against all potential risks.

Blood Sampling (fasting and during meal test)
There is minimal risk of bruising and infection associated with the blood draw and IV placement.

Medication
<u>Expected Adverse Events – Exenatide Extended-Release</u>
The long-acting, extended-release formulation of exenatide will be utilized for this trial. Despite a much lower incidence of nausea and vomiting, the magnitude of weight reduction with exenatide extended-release has been shown to be very similar to the twice per day formulation

in multiple trials. Exenatide extended-release is administered one time per week by subcutaneous injection in the upper arm, abdomen, or thigh. Exenatide will be initiated and maintained at a dose of 2.0 mg per week. The 2.0 mg dose was previously shown to achieve plasma exenatide concentrations similar to the maximum concentration achieved with a single injection of 10 mcg exenatide and was demonstrated to be the most efficacious dose for weight loss – a dose of 0.8 mg elicited no weight loss at 15 weeks in adults with T2DM. Exenatide extended-release and matching placebo pens will be provided by Astra Zeneca Pharmaceuticals. Placebo and active exenatide devices will be indistinguishable.

Study drug and placebo will be housed, dispensed, and tracked in the University of Minnesota Investigational Drug Service Pharmacy. Subjects will be given identical administration instructions regardless of group assignment. Instructive education will include reviewing procedures with a trained study coordinator and/or physician. Subjects will be instructed to administer the medication under the supervision of a parent/guardian. Subjects will be required to complete a study medication log.

Adverse events will be carefully and comprehensively reviewed and documented at each study visit and during each phone call (adverse events will be monitored monthly throughout the study). Subjects will be instructed to contact study staff immediately if any adverse event is experienced. Overall, the safety profile of exenatide is favorable, with nausea as the most commonly reported side effect. The metabolic effects of exenatide are triggered by the presence of food in the gut (i.e., glucose-dependent); therefore, the risk of hypoglycemia is extremely low when used as a mono-therapy, as will be the case in the proposed study. Mild injection site reactions (bruising, injection site pain, etc.) have ranged from 2-8% in studies with exenatide extended-release.

Evidence is mixed regarding whether acute pancreatitis and other potential pancreatic issues are associated with the use of GLP-1 receptor agonists among adult patients with T2DM. In the proposed study, we will minimize any potential risk of pancreatitis by excluding patients with T2DM, a disease known to be associated with an increased risk of pancreatitis. Furthermore, we will carefully monitor for reports of abdominal pain at each visit, and will measure lipase (pancreatic enzyme). Regarding potential associations of GLP-1 receptor agonists and pancreatic issues, the FDA and European Medicines Agency released communications in the summer of 2013 stating that available data do not confirm recent concerns over an increased risk for pancreatic side effects with GLP-1 based therapies.

11.5 Protections Against Risk

Claudia Fox, M.D., M.P.H., a pediatrician who is board-certified in obesity medicine, will be responsible for the medical safety aspects of this trial. Participants will be evaluated at each visit for potential side effects. Participants will be contacted by phone between visits to monitor and assess possible side effects and to encourage adherence to the medication regimen. At each contact with the participant and their parent/guardian, adverse events will be assessed by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event form. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document and will be grouped under one diagnosis. All adverse events occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event

that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

Calcitonin, amylase, lipase, prolactin, TSH, FSH, LH, testosterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), and carcinoembryonic antigen (CEA) will be measured throughout the study. Participants who at any time have a level of calcitonin exceeding 50 ng/L will be immediately withdrawn from the study. Sexual maturation and stature will be tracked throughout the study. Bone mineral content will be measured by iDXA and bone age via x-ray. Of note, we do not expect to observe an interaction between exenatide treatment and bone maturation but believe it is an important variable to measure in a pediatric drug trial. Duration of the QTc interval will be measured by ECG. Gastrointestinal side effects (mainly nausea) and other adverse events will be monitored monthly via regular phone calls by the study coordinator. Quantitative grading of the incidence and severity of gastrointestinal side effects will be conducted with the PedsQL Gastrointestinal Symptoms Scale at each study visit. A comprehensive metabolic panel will be performed at baseline and all post-randomization study visits.

11.6 Potential Benefits of the Proposed Research to the Subjects and Others

We believe the potential benefits (the prospect of benefit exists in that half of the participants will receive exenatide, which may reduce BMI and improve risk factors) to the participants outweigh the risks in this study. Since data from clinical trials in adults and evidence from our own research in adolescents with severe obesity have demonstrated reduction in BMI and improvements in cardiometabolic risk factors with exenatide, it is reasonable to expect similar results in the proposed clinical trial. The side effect profile of exenatide is favorable and the proposed tests are not more than minimal risk. The alternative treatment approach is standard-of-care lifestyle/behavioral modification therapy and/or treatment with orlistat or “off-label” weight loss medications. All participants in this study will receive lifestyle/behavioral modification therapy. Based upon data in adults and our preliminary evidence in adolescents, it is possible that the benefits of exenatide will be additive to the lifestyle/behavioral modification therapy.

11.7 Importance of the Knowledge to be Gained

Early development of cardiovascular disease and type 2 diabetes may be preventable if targeted interventions can be instituted early in life in adolescents who are at the greatest risk. Lifestyle modification, focusing on weight loss and increased physical activity, should be the foundational approach to treating severe obesity in adolescents. However, most adolescents with severe obesity are unable to reduce their weight to an acceptable level with lifestyle modification alone and may benefit from adjunctive pharmacotherapy to reduce adiposity and the risk of developing cardiovascular disease and type 2 diabetes. Few weight loss medications have been evaluated in obese adolescents and novel approaches should be explored. Data obtained from this study will determine whether exenatide is a safe and effective treatment for weight loss maintenance and sustained improvements in cardiometabolic risk factors among adolescents with severe obesity.

11.8 Data and Regulatory Monitoring Plan

Medical Monitoring

Safety monitoring will include careful assessment and appropriate reporting of adverse events. Adverse events will be monitored closely and subjects will be provided with information about the risks/side effects of the study medication and provided with phone numbers to reach the principal investigator/study coordinator in case of emergencies.

Study Monitoring
The study will undergo regular monitoring (annually during the enrollment and follow up period) of the facility, staff, and study documents by clinical research associates in the University of Minnesota Clinical Trials Monitoring Service, which specializes in regulatory compliance for clinical trials associated with the Food and Drug Administration. This service provides regular monitoring of all research-related activities and is offered free of charge through the University of Minnesota CTSI. Monitoring staff will present a summary report to the PI after each site visit. If necessary, corrective action plans will be devised and implemented by the PI to address deficiencies.

12 Study Finances

12.1 Funding Source

The study is funded by the National Institutes of Health (NIH) through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must refer to the Regents Policies on Individual Conflict of Interest Policy or Institutional Conflict of Interest Policy. These policies require University Faculty and staff to report external professional activities and business and significant financial interests related to his or her University activities by submitting a REPA (Report of External Professional Activities) at least once per year. Faculty and staff should also file a REPA when substantial changes in business or financial interests occur, when an activity that presents a potential conflict of interest is anticipated, or when submitting an application for research support or technology transfer, submitting research protocols to the IRB, or receiving financial contributions. All University of Minnesota investigators will follow the University conflict of interest policy.

Dr. Kelly serves as a consultant for Novo Nordisk pharmaceuticals and Takeda pharmaceuticals but does not accept personal or professional payment for his services. None of the other investigators have relevant conflicts to report.

12.3 Subject Stipends or Payments

Participants will receive a total of $1,400 in the form of gift cards if they complete all study visits (10 visits total). In addition, if applicable, parking and/or meal vouchers will be provided at each visit. Participants who are withdrawn early from study participation will be paid for the visits completed to that point.

13 Publication Plan

Data from this trial may be published. Dr. Aaron Kelly holds the primary responsibility for the publication of these data.

14 Reference List

Reference List

(1) Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med* 1995 March 9;332(10):621-8.

(2) MacLean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the impetus for weight regain. *Am J Physiol Regul Integr Comp Physiol* 2011 September;301(3):R581-R600.

(3) Sumithran P, Prendergast LA, Delbridge E et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med* 2011 October 27;365(17):1597-604.

(4) Danielsson P, Kowalski J, Ekblom O, Marcus C. Response of severely obese children and adolescents to behavioral treatment. *Arch Pediatr Adolesc Med* 2012 December;166(12):1103-8.

(5) Johnston CA, Tyler C, Palcic JL, Stansberry SA, Gallagher MR, Foreyt JP. Smaller weight changes in standardized body mass index in response to treatment as weight classification increases. *J Pediatr* 2011 April;158(4):624-7.

(6) Kalarchian MA, Levine MD, Arslanian SA et al. Family-based treatment of severe pediatric obesity: randomized, controlled trial. *Pediatrics* 2009 October;124(4):1060-8.

(7) Knop C, Singer V, Uysal Y, Schaefer A, Wolters B, Reinehr T. Extremely obese children respond better than extremely obese adolescents to lifestyle interventions. *Pediatr Obes* 2013 December 17.

(8) Kelly AS, Barlow SE, Rao G et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation* 2013 October 8;128(15):1689-712.

(9) Skinner AC, Skelton JA. Prevalence and Trends in Obesity and Severe Obesity Among Children in the United States, 1999-2012. *JAMA Pediatr* 2014 April 7.

(10) Freedman DS, Mei Z, Srinivasan SR, Berenson GS, Dietz WH. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. *J Pediatr* 2007 January;150(1):12-7.

(11) Urbina EM, Kimball TR, McCoy CE, Khoury PR, Daniels SR, Dolan LM. Youth with obesity and obesity-related type 2 diabetes mellitus demonstrate abnormalities in carotid structure and function. *Circulation* 2009 June 9;119(22):2913-9.

(12) Norris AL, Steinberger J, Steffen LM, Metzig AM, Schwarzenberg SJ, Kelly AS. Circulating Oxidized LDL and Inflammation in Extreme Pediatric Obesity. *Obesity (Silver Spring)* 2011 July;19(7):1415-9.

(13) Kelly AS, Metzig AM, Schwarzenberg SJ, Norris AL, Fox CK, Steinberger J. Hyperleptinemia and hypoadiponectinemia in extreme pediatric obesity. *Metab Syndr Relat Disord* 2012 April;10(2):123-7.

(14) Kelly AS, Hebbel RP, Solovey AN et al. Circulating activated endothelial cells in pediatric obesity. *J Pediatr* 2010 October;157(4):547-51.

(15) Burns TL, Letuchy EM, Paulos R, Witt J. Childhood predictors of the metabolic syndrome in middle-aged adults: the Muscatine study. *J Pediatr* 2009 September;155(3):S5-26.

(16) Freedman DS, Patel DA, Srinivasan SR et al. The contribution of childhood obesity to adult carotid intima-media thickness: the Bogalusa Heart Study. *Int J Obes (Lond)* 2008 May;32(5):749-56.

(17) Raitakari OT, Juonala M, Kahonen M et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA* 2003 November 5;290(17):2277-83.

(18) Franks PW, Hanson RL, Knowler WC et al. Childhood predictors of young-onset type 2 diabetes. *Diabetes* 2007 December;56(12):2964-72.

(19) McCance DR, Pettitt DJ, Hanson RL, Jacobsson LT, Bennett PH, Knowler WC. Glucose, insulin concentrations and obesity in childhood and adolescence as predictors of NIDDM. *Diabetologia* 1994 June;37(6):617-23.

(20) Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. *J Pediatr* 2008 February;152(2):201-6.

(21) Nguyen QM, Srinivasan SR, Xu JH, Chen W, Berenson GS. Changes in risk variables of metabolic syndrome since childhood in pre-diabetic and type 2 diabetic subjects: the Bogalusa Heart Study. *Diabetes Care* 2008 October;31(10):2044-9.

(22) Nguyen QM, Srinivasan SR, Xu JH, Chen W, Kieltyka L, Berenson GS. Utility of childhood glucose homeostasis variables in predicting adult diabetes and related cardiometabolic risk factors: the Bogalusa Heart Study. *Diabetes Care* 2009 December 15.

(23) Srinivasan SR, Myers L, Berenson GS. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: the Bogalusa Heart Study. *Diabetes* 2002 January;51(1):204-9.

(24) Thearle MS, Bunt JC, Knowler WC, Krakoff J. Childhood predictors of adult acute insulin response and insulin action. *Diabetes Care* 2009 May;32(5):938-43.

(25) Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of changes in glucose tolerance status in obese youth. *Diabetes Care* 2005 April;28(4):902-9.

(26) Yeung EH, Zhang C, Louis GM, Willett WC, Hu FB. Childhood size and life course weight characteristics in association with the risk of incident type 2 diabetes. *Diabetes Care* 2010 June;33(6):1364-9.

(27) Invitti C, Guzzaloni G, Gilardini L, Morabito F, Viberti G. Prevalence and concomitants of glucose intolerance in European obese children and adolescents. *Diabetes Care* 2003 January;26(1):118-24.

(28) Sinha R, Fisch G, Teague B et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002 March 14;346(11):802-10.

(29) Weiss R, Dziura J, Burgert TS et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004 June 3;350(23):2362-74.

(30) Kitahara CM, Flint AJ, Berrington de GA et al. Association between Class III Obesity (BMI of 40-59 kg/m2) and Mortality: A Pooled Analysis of 20 Prospective Studies. *PLoS Med* 2014 July;11(7):e1001673.

(31) Astrup A, Caterson I, Zelissen P et al. Topiramate: long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. *Obes Res* 2004 October;12(10):1658-69.

(32) Early JL, Apovian CM, Aronne LJ et al. Sibutramine plus meal replacement therapy for body weight loss and maintenance in obese patients. *Obesity (Silver Spring)* 2007 June;15(6):1464-72.

(33) Wadden TA, Fujioka K, Toubro S et al. A randomized trial of lifestyle modification and taranabant for maintaining weight loss achieved with a low-calorie diet. *Obesity (Silver Spring)* 2010 December;18(12):2301-10.

(34) Wadden TA, Hollander P, Klein S et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)* 2013 November;37(11):1443-51.

(35) Grill HJ, Hayes MR. The nucleus tractus solitarius: a portal for visceral afferent signal processing, energy status assessment and integration of their combined effects on food intake. *Int J Obes (Lond)* 2009 April;33 Suppl 1:S11-S15.

(36) Bojanowska E. Physiology and pathophysiology of glucagon-like peptide-1 (GLP-1): the role of GLP-1 in the pathogenesis of diabetes mellitus, obesity, and stress. *Med Sci Monit* 2005 August;11(8):RA271-RA278.

(37) Edwards CM, Stanley SA, Davis R et al. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab* 2001 July;281(1):E155-E161.

(38) Alhadeff AL, Grill HJ. Hindbrain nucleus tractus solitarius glucagon-like peptide-1 receptor signaling reduces appetitive and motivational aspects of feeding. *Am J Physiol Regul Integr Comp Physiol* 2014 June 18.

(39) Alhadeff AL, Baird JP, Swick JC, Hayes MR, Grill HJ. Glucagon-like Peptide-1 receptor signaling in the lateral parabrachial nucleus contributes to the control of food intake and motivation to feed. *Neuropsychopharmacology* 2014 August;39(9):2233-43.

(40) Anderberg RH, Anefors C, Bergquist F, Nissbrandt H, Skibicka KP. Dopamine signaling in the amygdala, increased by food ingestion and GLP-1, regulates feeding behavior. *Physiol Behav* 2014 February 21.

(41) Dickson SL, Shirazi RH, Hansson C, Bergquist F, Nissbrandt H, Skibicka KP. The glucagon-like peptide 1 (GLP-1) analogue, exendin-4, decreases the rewarding value of food: a new role for mesolimbic GLP-1 receptors. *J Neurosci* 2012 April 4;32(14):4812-20.

(42) Horowitz M, Flint A, Jones KL et al. Effect of the once-daily human GLP-1 analogue liraglutide on appetite, energy intake, energy expenditure and gastric emptying in type 2 diabetes. *Diabetes Res Clin Pract* 2012 August;97(2):258-66.

(43) Steinert RE, Schirra J, Meyer-Gerspach AC et al. Effect of glucagon-like peptide-1 receptor antagonism on appetite and food intake in healthy men. *Am J Clin Nutr* 2014 June 25;100(2):514-23.

(44) van CJ, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Int J Obes (Lond)* 2014 June;38(6):784-93.

(45) Yang Y, Moghadam AA, Cordner ZA, ChuLiang N, Moran TH. Long term exendin-4 treatment reduces food intake and body weight and alters expression of brain homeostatic and reward markers. *Endocrinology* 2014 June 20;en20141052.

(46) Zhao S, Kanoski SE, Yan J, Grill HJ, Hayes MR. Hindbrain leptin and glucagon-like-peptide-1 receptor signaling interact to suppress food intake in an additive manner. *Int J Obes (Lond)* 2012 December;36(12):1522-8.

(47) Astrup A, Carraro R, Finer N et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)* 2012 June;36(6):843-54.

(48) Beglinger S, Meyer-Gerspach AC, Graf S et al. Effect of a test meal on meal responses of satiation hormones and their association to insulin resistance in obese adolescents. *Obesity (Silver Spring)* 2014 June 13.

(49) Chaudhuri A, Ghanim H, Vora M et al. Exenatide exerts a potent antiinflammatory effect. *J Clin Endocrinol Metab* 2012 January;97(1):198-207.

(50) Kelly AS, Metzig AM, Rudser KD et al. Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. *Obesity (Silver Spring)* 2012 February;20(2):364-70.

(51) Koska J, Schwartz EA, Mullin MP, Schwenke DC, Reaven PD. Improvement of postprandial endothelial function after a single dose of exenatide in individuals with impaired glucose tolerance and recent-onset type 2 diabetes. *Diabetes Care* 2010 May;33(5):1028-30.

(52) Okerson T, Yan P, Stonehouse A, Brodows R. Effects of exenatide on systolic blood pressure in subjects with type 2 diabetes. *Am J Hypertens* 2010 March;23(3):334-9.

(53) Yamazaki S, Satoh H, Watanabe T. Liraglutide Enhances Insulin Sensitivity by Activating AMP-Activated Protein Kinase in Male Wistar Rats. *Endocrinology* 2014 June 20;en20132157.

(54) Kelly AS, Rudser KD, Nathan BM et al. The effect of glucagon-like Peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity: a randomized, placebo-controlled, clinical trial. *JAMA Pediatr* 2013 April 1;167(4):355-60.

(55) Berkowitz RI, Wadden TA, Gehrman CA et al. Meal replacements in the treatment of adolescent obesity: a randomized controlled trial. *Obesity (Silver Spring)* 2011 June;19(6):1193-9.

(56) Inge TH, Zeller MH, Jenkins TM et al. Perioperative outcomes of adolescents undergoing bariatric surgery: the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study. *JAMA Pediatr* 2014 January;168(1):47-53.

(57) Heymsfield SB, van Mierlo CA, van der Knaap HC, Heo M, Frier HI. Weight management using a meal replacement strategy: meta and pooling analysis from six studies. *Int J Obes Relat Metab Disord* 2003 May;27(5):537-49.

(58) Bandini LG, Schoeller DA, Cyr HN, Dietz WH. Validity of reported energy intake in obese and nonobese adolescents. *Am J Clin Nutr* 1990 September;52(3):421-5.

(59) Bergenstal RM, Wysham C, MacConell L et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 2010 June 25.

(60) Buse JB, Drucker DJ, Taylor KL et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care* 2010 June;33(6):1255-61.

(61) Diamant M, Van GL, Stranks S et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet* 2010 June 26;375(9733):2234-43.

(62) Kim D, MacConell L, Zhuang D et al. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. *Diabetes Care* 2007 June;30(6):1487-93.

(63) Pickering TG, Hall JE, Appel LJ et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation* 2005 February 8;111(5):697-716.

(64) Design of a family-based lifestyle intervention for youth with type 2 diabetes: the TODAY study. *Int J Obes (Lond)* 2010 February;34(2):217-26.

(65) Carnell S, Wardle J. Measuring behavioural susceptibility to obesity: validation of the child eating behaviour questionnaire. *Appetite* 2007 January;48(1):104-13.

(66) Mallan KM, Liu WH, Mehta RJ, Daniels LA, Magarey A, Battistutta D. Maternal report of young children's eating styles. Validation of the Children's Eating Behaviour Questionnaire in three ethnically diverse Australian samples. *Appetite* 2013 May;64:48-55.

(67) Sleddens EF, Kremers SP, Thijs C. The children's eating behaviour questionnaire: factorial validity and association with Body Mass Index in Dutch children aged 6-7. *Int J Behav Nutr Phys Act* 2008;5:49.

(68) Wardle J, Guthrie CA, Sanderson S, Rapoport L. Development of the Children's Eating Behaviour Questionnaire. *J Child Psychol Psychiatry* 2001 October;42(7):963-70.

(69) Flint A, Raben A, Blundell JE, Astrup A. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *Int J Obes Relat Metab Disord* 2000 January;24(1):38-48.

(70) Sysko R, Devlin MJ, Schebendach J et al. Hormonal responses and test meal intake among obese teenagers before and after laparoscopic adjustable gastric banding. *Am J Clin Nutr* 2013 November;98(5):1151-61.

(71) Chandler-Laney PC, Higgins PB, Granger W et al. Use of a simple liquid meal test to evaluate insulin sensitivity and beta-cell function in children. *Pediatr Obes* 2014 April;9(2):102-10.

(72) Chase HP, Lutz K, Pencek R, Zhang B, Porter L. Pramlintide lowered glucose excursions and was well-tolerated in adolescents with type 1 diabetes: results from a randomized, single-blind, placebo-controlled, crossover study. *J Pediatr* 2009 September;155(3):369-73.

(73) Roffey DM, Byrne NM, Hills AP. Day-to-day variance in measurement of resting metabolic rate using ventilated-hood and mouthpiece & nose-clip indirect calorimetry systems. *JPEN J Parenter Enteral Nutr* 2006 September;30(5):426-32.

(74) Segal KR. Comparison of indirect calorimetric measurements of resting energy expenditure with a ventilated hood, face mask, and mouthpiece. *Am J Clin Nutr* 1987 June;45(6):1420-3.

(75) Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA* 2007 July 11;298(2):194-206.

(76) Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. *Diabetes Res Clin Pract* 2012 November;98(2):271-84.

(77) Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care* 2010 November;33(11):2349-54.

(78) Romley JA, Goldman DP, Solomon M, McFadden D, Peters AL. Exenatide therapy and the risk of pancreatitis and pancreatic cancer in a privately insured population. *Diabetes Technol Ther* 2012 October;14(10):904-11.

(79) Wenten M, Gaebler JA, Hussein M et al. Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. *Diabet Med* 2012 November;29(11):1412-8.

(80) Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011 July;141(1):150-6.

(81) Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike Peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med* 2013 April 8;173(7):534-9.