Glucagon-Like Peptide-1 Agonist Effects on Energy Balance in Hypothalamic Obesity (ECHO - Energy Balance in Craniopharygioma with Hypothalamic Obesity)

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RESEARCH PROTOCOL

1. STUDY SITES:

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2. PROJECT TITLE

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3. INTRODUCTION

Background/Significance

Excessive weight gain and its cardiometabolic sequela are frequent complications of hypothalamic tumors, a condition known as hypothalamic obesity (HO). Most tumors in this region are craniopharyngiomas (CP),[1] which constitute 5–9% of childhood brain tumors.[2,3] Patients with CP typically become obese and have more features of the metabolic syndrome compared to matched controls.[4,5] Overall, a 3-19-fold higher cardiovascular mortality had been reported,[6,7] and a recent nationwide population-based study in Sweden demonstrated increased rates for cerebral infarction (7-fold), death due to cerebrovascular diseases (5-fold), and type 2 diabetes mellitus (6-fold) in CP patients in comparison to the general population.[8] Thus, early and effective management of obesity is vital for this population,[9] which is more resistant to treatment than uncomplicated obesity.[10-18] Recognized risk factors for severe obesity include large hypothalamic tumors or lesions affecting several medial and posterior hypothalamic nuclei that impact satiety signaling pathways.[19, 26-28] Structural damage in these nuclei often lead to uncontrolled appetite, rapid weight gain, central insulin and leptin resistance, decreased sympathetic activity, low energy expenditure (EE), and increased energy storage in adipose tissue.[13,19] Recently, our group developed a *semi-quantitative assessment of hypothalamic damage on brain magnetic resonance imaging (MRI) to predict the risk for HO development in CP*.[26]

Previous results of treating HO with a glucagon-like-peptide-1 receptor agonist (GLP1RA) in rats[20] and humans[21,22] provide promising proof-of-principle data to support our randomized clinical trial. Our primary hypothesis is that drugs causing weight loss via intact hindbrain signaling pathways offer a desperately needed option for treatment of HO, even in very obese HO subjects with severe hypothalamic damage. Induction of weight loss by GLP1RAs is believed to be related to multiple mechanisms involving the gastrointestinal tract, vagus nerve, and the brain leading to increased satiety.[23-28] Peripheral administration of GLP-1 or GLP1RA reduces blood glucose and energy intake in humans and rodents, and long-term treatment results in loss of body weight.[23,29-45] Critically, we do not know whether GLP1RA treatment affects EE and activity,[46-49] or whether the site and size of brain lesions affect responses to GLP1RA treatment.

Our previous clinical studies of the GLP1RA exenatide in obese adolescents and adults have generated the critical safety and efficacy data needed to design a clinical trial.[21,22,50] In a pilot study conducted at Children's Hospitals and Clinics of MN, pretreatment hyperphagia was associated with BMI reduction. Using these data, we have designed a prospective, multicenter trial that will examine the effects of GLP1RA on BMI, cardiovascular disease (CVD) risk factors, energy homeostasis and other factors in subjects with HO secondary to CP or other hypothalamic tumors.

4. STUDY DESIGN AND METHODOLOGY

Specific Aims and Hypotheses

Specific Aim 1: To test effects of GLP1RA on hypothalamic obesity prospectively. *We hypothesize that treatment with GLP1RA will significantly reduce adiposity in patients with HO. We furthermore hypothesize that GLP1RA treatment will lead to increased satiety.* To this end, we propose to conduct a double blind, placebo-controlled, randomized trial of once weekly extended release exenatide (ExQW) on metabolic and clinical outcomes. Following baseline testing, 48 patients (10-25y at time of enrollment) with HO will be randomly assigned with equal allocation to ExQW or matching placebo injection for 36 weeks, followed by an 18-week open label extension during which all patients will receive ExQW. Our primary endpoint is percent change in BMI after 36 weeks. Secondary endpoints will include changes in body fat, and satiety by free buffet meal test.

Specific Aim 2: To determine effects of GLP1RA on cardiometabolic risk factors. *We hypothesize that GLP1RA will also lead to (1) favorable changes in blood glucose, lipid profile, and inflammatory marker, and (2) reduced insulin secretion during an oral glucose tolerance test.* In the same cohort, we will examine changes in blood glucose, lipid profile, inflammatory markers, and insulin resistance by testing insulin secretion during an oral glucose tolerance test after adjustment for glucose response and adiposity.

Specific Aim 3: To explore additional outcome measures, and predictors of treatment responses. HO represents a disorder of energy homeostasis.

Aim 3 A: *To test the hypothesis that GLP1RA will normalize homeostasis by increasing EE in relation to energy intake*. This and prior hypotheses allow us to test potential predictors of treatment outcomes.

Aim 3 B: *To test the hypotheses that (1) a lower hypothalamic lesion score and (2) lower fasting serum leptin as well as (3) higher pretreatment hyperphagia will be associated with better BMI outcomes.* The study will include brain lesion scoring, behavioral and hormonal measures, free-living total daily energy expenditure by doubly labeled water (DLW), energy intake by 24h dietary recall, and activity by actigraphy.

Overview/Scope

Study Design

The proposed study is a multi-site 36-week double-blind, placebo-controlled randomized trial followed by an 18-week open label extension with all patients receiving the GLP1RA treatment. Therefore, each subject will be treated for a total of 54 wk. Subjects will be required to travel to one of three research sites (Seattle, Nashville, St. Paul). A flowchart for scheduled study visits (SVs) is outlined below. Before study start, there will be an investigator kickoff and training meeting guided by Dr. Yanovski from Seattle Children's to coordinate and align all assessments and interventions. In addition, Seattle Children's radiology center will provide standardized protocols to the other two imaging centers for consistent imaging techniques and analyses. During the study and after ending the intervention, there will be bimonthly investigator phone or video conferences.

Time Frame/Duration

The timeline for research activities is four years. This is outlined as: Years 1-3: Enrollment and treatment at 3 study sites. Years 3 and 4: hormonal assays. Year 4: completion of final data analyses.

Each patient will be in the study for 56 weeks, including the screening visit.

Data Requirements

A database will be designed for this study using REDCap (Research Electronic Data Capture) hosted at the Institute of Translational Health Sciences of which Seattle Children's and University of Washington are partners. REDCap is a secure, web-based application designed to support data capture for research studies, providing validated data entry, audit trails, and mechanisms for securely importing and exporting data. It will reside on a secure server with exclusive access by research personnel at all study sites. Access is tailored for specific roles to maintain blinding. Subjects are identified with a study identification number.

Study Measures

Anthropometric measures. Anthropometric measurements including height, weight, waist, and hip circumference as well as Tanner pubertal staging will be collected (see Fig. 1) at every visit (except 6 weeks). Anthropometric measures were selected based on (1) prior demonstration as a predictor of child outcomes in pediatric weight control, and (2) being measures of treatment change. Weight and height: Participant height will be assessed as the average of three repeated measures using a calibrated stadiometer. Weight will be assessed in light clothing as the average of three repeated measures on a calibrated electronic scale. In addition, we will measure waist and hip circumference. We will take all measurements three times according to guidelines (http://www.cdc.gov/nchs/nhanes.htm) and record the average measurements. Heart rate (HR) and resting office blood pressure (BP) will be measured with an aneroid sphygmomanometer according guidelines of the National High Blood Pressure Education Program,[51] as successfully used in other multicenter pediatric studies.[52] Body fat assessment: BMI will be calculated as kg/m^2. We will use % change in BMI to allow for comparison over various age groups. Dual energy x-ray absorptiometry (DEXA) will be adjusted for height, age, sex, and race as covariates, and used to measure body fat as an additional descriptive parameter for adiposity.

Energy expenditure measures. There is no previous study examining the impact of GLP1RA treatment on EE in subjects with CP, a population suffering from decreased resting metabolic rate and physical activity.[53-56] **Total daily energy expenditure** (total EE, kcal/day) will be measured using doubly labeled water (DLW). Total EE comprises resting metabolic rate, thermic effect of meals, and physical activity EE. All three components can be accurately determined by using the gold standard method, DLW under free living conditions over a period of two wk.[57,58] Through periodic urine collection, DLW estimates carbon dioxide production by measuring the elimination of the tracers deuterium (^2H) and oxygen-18 (^{18}O) from the body.[47] The DLW is a reference method for measurements of average total EE for a period of 10-14 days in free-living individuals tested in a variety of pediatric[59-61] and adult[62] populations, and individuals with various diseases.[63-65] The DLW protocol will be coordinated by the Energy Balance Laboratory at Vanderbilt University (M. Buchowski – Director, see letter of support) in collaboration with the Gas-Isotope-Ratio Mass Spectrometry Laboratory at Baylor College of Medicine's USDA/ARS Children's Nutrition Research Center (DLW Lab - Dr. W. Wang, Director). Participants from all sites will receive a DLW sample and will collect urine according to the protocol schedule. Baseline urine samples will be collected at the clinic visits while day 7 and day 14 samples will be mailed from home. After drinking the doubly labeled water at the site, subjects will be instructed to rinse the glass and to drink the rinse water; they will be asked to repeat this step (rinsing and drinking a total of two times). They will be asked to void and the urine sample will be discarded. The next two patient voids (at 2 hours and 6 hours) will be collected for isotope analysis (deuterium and ^{18}O) at Baylor University. Urine samples will be collected at day 7 and day 14 for isotope analysis.

Physical activity. In one of our prior studies with CP patients, we assessed physical activity by accelerometry.[54] In the proposed study, subjects' physical activity will be measured by the Actigraph GT3M accelerometer, worn on the non-dominant wrist. To measure activity and sleep duration, subjects will wear the actigraph monitor continuously for 2 wk. Drs. Roth[54] and Shoemaker have used these devices before. The actigraphs used are small and unobtrusive, and can provide a reliable and valid estimate of children's moderate-to-vigorous physical activity.[66-70] Accelerometer data will be categorized into time spent in sedentary, as well as light, moderate, and vigorous activity using calibration thresholds specifically for children.[69,71,72] The Physical Activity Checklist Interview,[73-75] will be used to complement actigraphy data with descriptive self-reported assessments of physical activity.

Behavioral, and psychosocial measures. Energy intake will be assessed by *Automated Self-Administered 24-Hour Dietary Recall* (ASA24-Kids, http://appliedresearch.cancer.gov/tools/instruments/asa24/), which is a validated web-based free method of a 24h dietary recall for children 10 y and older which will be performed at two time points around study visits 0, 18, 36 and 54 wk. At 0, 18 and 36 wk subject's parents will furthermore complete the *Child Eating Behavior Questionnaire* (CEBQ),[76] or the Adult Eating Behavior Questionnaire (AEBQ) which measures positive and negative eating behaviors (food responsiveness, enjoyment of food, emotional overeating, desire to drink, satiety responsiveness, slowness in eating, emotional undereating and fussiness) and the *Hyperphagia Questionnaire*[77], a 13- item questionnaire developed for use in patients with Prader-Willi syndrome but that has also been used to study hyperphagic behavior in other populations.[78-80] These are all validated questionnaires and we have used them in previous studies.

Meal test. At study visits 1, 3 and 4 (0, 18 and 36 wk), subjects will have an OGTT (900-1100 AM) in the fasting condition, followed at study visits 0 and 36 wk by a standardized mixed meal caloric preload (macaroni & cheese at 1100 AM) and a free buffet meal (at 1230 PM). The buffet meal is an objective measure of satiety as it assesses food intake and choice after a caloric preload. The standardized test meal preload will provide 12%of estimated daily caloric requirements,[81] based on the Schofield-HW equation.[82] The purpose of the test meal is to ensure that study participants are in an equally fed state (together with oral glucose, total preload will be 22-27% of estimated daily caloric intake). Ninety minutes later, an ad libitum buffet meal will be served consisting of a wide variety of food items and more than the child's estimated daily calorie requirements will be offered (5,000 kcal). Participants will have access to the buffet for 30 min, after which calorie intake and composition of consumed foods will be measured by weighing back uneaten food. Hunger and fullness will be assessed every 30 min from fasting state before starting the OGTT until the end of the buffet meal using visual analog scales (VAS)[83] to assess subjective appetite, reliable in children over age 7 y,[84] and used by us previously.[85]

Metabolic outcomes. Blood glucose, insulin, lipid panel, hemoglobin A1c, and as a measure of low-grade inflammation C-reactive protein will be assessed by high-sensitive (hsCRP) testing at a central lab (Northwest Lipid Research Laboratories, Seattle). Glucose tolerance will be assessed by a 2-hour oral glucose tolerance test. After placement of an intravenous catheter (IV), a baseline blood sample will be collected for measurement of hemoglobin A1C, and insulin (processed by the central lab). A 2-h OGTT (1.75 g/kg Glucola [maximum 75 g]) will then be performed with sample collection at 0', 30', 60', 90' and 120' for measurement of glucose and insulin. Samples will be placed on ice, and will be centrifuged. Leptin, total adiponectin, α-MSH, and soluble leptin receptor (sOB-R) are potential indicators of leptin sensitivity,[86-89] and will be assessed in fasting state (leptin, total adiponectin, and sOB-R, R&D Systems, Minneapolis, MN; α-MSH, Phoenix Pharmac., Belmont, CA, the assay cross

reacts 100% with amidated and acylated α-MSH and 79% with des-acylated α-MSH). The leptin to adiponectin ratio provides information regarding the risk of metabolic syndrome.[90-93] All endocrine measures will be performed at the PI's lab at Seattle Children's Research Institute. In our laboratory, intra-assay coefficients of variation (CV) are <8%, and inter-assay CVs are <10% for these methods. For all assays, all samples will be run in duplicate.

OGTT derived measures. The assessment of dynamic changes of glucose and insulin secretion has clear advantages over static tests such as fasting insulin and glucose levels. Calculation models have been established for using OGTT insulin and glucose data to calculate first and second phase insulin secretion that correlate well with clamp data, and give surrogates for β-cell function and insulin sensitivity.[94-97] In our study, we will assess insulin sensitivity by whole body insulin sensitivity index (WBISI) that encompasses both hepatic and peripheral tissue insulin sensitivity.[98] As exploratory outcome parameters, the first phase insulin response to oral glucose will be calculated by insulinogenic index (IGI), which is a surrogate of the β-cell function,[95] using the formula: IGI = ($Ins_{30\ min}$-Ins_{0min})/($Gluc_{30\ min}$-$Gluc_{0min}$).[94] Insulin resistance will be also estimated by homeostasis model assessment of insulin resistance (HOMA-IR).[99] Change in glucose metabolism parameters will be adjusted to ΔBMI.

Neuroimaging analysis. At all sites, 3T protocols will be standardized to yield anatomical resolution of 1 mm^3 for T1 volumetric images and identical in-place resolution at 2 mm slice thickness for T2-weighted series. These parameters are substantially improved compared to *in vivo* 1.5T (3 mm resolution) work of Makris[100] in which a segmentation method for hypothalamus subregions using 7T scans of *ex vivo* pathological specimens was developed as a template. We will assess the topographic location and size of damaged brain areas using our established rating system, and also quantified measurement of residual lesion volume, ventricular volumes, and hypothalamic region volumes,[100] using a combination of ITK-SNAP[101] and MATLAB (Mathworks, Natick MA) for template creation as performed in our previous work.[102] From these rating images, we will assign brain damage to specific brain nuclei using the Brain Atlas from Mai et al.[103] We have found that this scoring system can be applied effectively even with mildly suboptimal (fair to good) image quality. We anticipate 40% of subjects to undergo MRI examination within 6 mo of week 0, precluding data-collection of a new MRI. Since Makris[100] made measurements on 3 mm images, probably the minimum spatial resolution that would ever be collected given current standard MRI scanner techniques, we do not anticipate this will impede scoring or quantifying lesion/hypothalamic region volume. Furthermore, where anatomical distortion creates deviations from the published rule-set for hypothalamic sub-regions, we will develop a new adaptive landmark approach to obtain an estimate of total lesion and hypothalamic sub-measurement. Given these acquired and measured variables, we anticipate rating and volumetric indices will be available for the entire sample precluding subjects where patient motion makes hypothalamic sub-region delineation challenging (anticipated to be 5%). All imaging studies, including those obtained at other facilities will be burned on CD and mailed to Seattle Children's to be analyzed by a single central reader blinded to treatment and clinical data (Dr. Perez, neuroradiologist at Seattle Children's) to determine presence and extent of hypothalamic involvement according to our scoring system and analytic methods proposed.

Drug/Device, Handling, Storage

The IND is: 122971

Rationale for Medication

Currently available GLP1RAs include a variety of schedules: twice daily (exenatide), once daily (liraglutide), and once weekly (exenatide, albiglutide, and dulaglutide). Alternatively, levels of native GLP-1 can be increased by inhibiting dipeptidyl peptidase 4 (DPP-4), a protease that rapidly degrades native GLP-1. However, DPP-4 inhibitors do not inhibit appetite or lead to body weight reduction. Liraglutide, the active ingredient in Saxenda®, was recently approved as a weight loss medication showing a 7.3% decrease in body weight over a 56 wk trial in adults with severe obesity.[104,105] However, this drug has not been made available for use in pediatric studies and this is not expected to change in the near future (personal communication with Medical Director, Obesity at Novo Nordisk Inc). Therefore, we decided to use the extended-release GLP-1 receptor agonist ExQW which is also advantageous as it requires only weekly injections, addressing some of the adherence and side effect issues that could pose barriers to therapy. This drug contains exenatide, which is a 39-amino-acid synthetic version of exendin-4 that shares approximately 50% sequence identity with human GLP-1. In previous studies of adults with T2DM, ExQW showed slightly larger reductions in body weight compared with twice daily exenatide, although this difference was statistically not different.[106] Mild to moderate GI adverse events were common in previously tested three GLP-1 agonists, and were least frequent with ExQW.[33,106-108] ExQW contains exenatide encapsulated in microspheres consisting of a medical-grade biodegradable poly-(d,l-lactide-co-glycolide) polymer, which has been used in other medical applications since 1984, and allows for slow, continuous release of the active agent into circulation following injection.[34,109] ExQW will be started at 2 mg subcutaneously once weekly. Treatment dosage and duration are based on prescribing information and prior successful clinical trial weight loss results.[31,110] The placebo-control group is an essential arm in this trial as study measures can change over time without drug intervention and it supports the evaluation of efficacy and safety. The drug and placebo kits will be supplied by AstraZeneca, or the current pharmacologic company responsible for ExQW. Exenatide vials or pens 2.0 mg powder for injection will be supplied. All subjects will have weekly phone calls when not coming for a study visit, to check adherence and any potential
adverse effects. Any evidence for adverse effects will be discussed with the PI of each site and safety clinical visits will be considered.

All study medication will be stored/locked in the investigational pharmacy under appropriate temperature conditions. Dispensing and accountability records will be maintained by appropriate staff members.

Analysis

Analysis plan and sample size calculations by Aim.

The research team includes personnel with statistical and data management expertise for overseeing data collection, storage methods, and the following analyses (see letter of support, Dr. Shaffer). Adherence data collected during the placebo run-in phase will be summarized descriptively. All subjects completing the run-in phase will go on to the randomized treatment phase. The primary analyses will use the intention-to-treat (ITT) approach; i.e., subjects will be analyzed according to their randomized assignment regardless of treatment received. In addition, data of all completers will be analyzed separately as a sensitivity analysis. While every attempt will be made to collect complete data and retain all subjects, all sample size and power calculations account for dropout. Statistical methods have been selected to allow for inclusion of partial data. All testing is two-sided and α=0.05. Repeated measures analyses will be conducted using SAS (SAS Institute, Inc., Cary, NC, USA) or R (The R Foundation for

Statistical Computing).

Analysis populations: All eligible subjects randomized will be included in the ITT population. The ITT population will be the primary analysis population for all primary, secondary, and tertiary outcomes. The safety population will be the primary population for all safety analyses, and include all subjects who receive at least one dose of study drug or placebo.

Table 1. Summary of Study Measures and Outcomes and Their Use in the Proposed Research				
Measure	**Domain**	**Instrument**	**Aim**	**Role/Application**
ΔBMI%	Adiposity	Anthropometry	1	**Primary outcome**
Total body fat mass	Body composition	DEXA	1	Secondary outcome
Fat and total calorie intake	Post test meal satiety assessment	Free buffet meal analysis	1	Secondary outcome
Glucose tolerance	Glucose tolerance, MetS	Glucose at 0', 120' (OGTT)	2	Secondary outcome
HDL, triglycerides	MetS	Fasting lipids	2	Secondary outcome
hsCRP	Inflammation	hsCRP at fasting time point	2	Secondary outcome
Free living EE	Energy homeostasis	Doubly labeled water	3	Tertiary outcome
Energy intake	Energy intake	24h dietary recall (ASA24)	3	Tertiary outcome
Leptin, adiponectin, sOB-R, α-MSH, HOMA-IR, WBISI	Energy homeostasis, leptin sensitivity, and insulin resistance	Baseline and stimulated hormones	3	Tertiary outcomes and predictors

Aim 1: To test effects of GLP1RA on hypothalamic obesity prospectively.

Sample: Available anthropometry measures will be included in the analyses (see also Fig. 1 below).

Primary outcome analysis: For efficacy analysis the primary outcome is % change in BMI from week 0 (baseline) to 36 wk. A piecewise (separating the randomized and run out phases) linear mixed-effects model[111] will be fit with % change in BMI from baseline to 36 wk as the outcome; treatment, time, and the interaction between treatment and time as factors of interest; and randomization stratification variables (site, age, and gender) included as covariates. This model is a generalization of analysis of covariance (ANCOVA) that allows all follow-up repeated measures to be included. Baseline BMI will be considered as an additional covariate. A spatial power within-subject correlation matrix will be used to account for the correlated repeated measures. Separate contrasts based on the interaction between treatment and time will be used to specifically test for a significant difference in % change in BMI from baseline to 36 wk post-treatment and 54 wk (end of open label extension). Additionally, descriptive summaries will be prepared for change in BMI z-score to supplement interpretation of findings. Study outcomes, their use, and descriptive parameters are in Tables 1 & 2.

Table 2. Additional Descriptive Parameters, Predictors and Covariates used in Study			
Measure	**Domain**	**Instrument**	**Aim**
ΔBMI, ΔBMI z-score	Adiposity	Anthropometry	1
Subjective appetite	Hunger and fullness rating	Visual analog scale	1
Syst. & diast. BP	CVD risk factor, MetS	Ambulatory BP	2
Exercise	Physical activity measure	Actigraphy [112,113]	3
Energy intake	Energy intake	24h dietary recall	3
Eating behavior	Assessment of overeating and food reward	Overeating (CEBQ),[76] & hyperphagia.[77]	3
Brain lesion score, hypothalamic region and residual lesion volumes	Structural lesion in the pituitary-hypothalamic area	Brain MRI images	3

Table 3 Aim	Outcome	Observed Δ Exenatide vs. Control	Observed pooled Std. Dev.	Observed relative effect size
1	% ΔBMI	-4.29	3.84	-1.12
1	Absolute ΔBMI	-1.74	1.25	-1.39
2	ΔGlucose AUC (per 100)	-29.36	26.44	-1.11
2	ΔInsulin (mU/L)	-7.62	7.14	-1.07

Sample size and power: Table 3 shows observed relative effect sizes in our preliminary study for the between-treatment comparison of change from baseline to 3 mo (data from previous study[22]). Assuming a normal distribution of changes, a type I error rate of 0.05, and a dropout rate of up to 20%, a sample size of 24 subjects per group (19 evaluable) will provide 85% power to detect relative treatment effect sizes of 1 or greater (in absolute value) for % change in BMI, which is consistent with the preliminary data.

Expected result: We expect GLP1RA treatment will reduce BMI (primary efficacy endpoint). Further we expect that GLP1RA treatment will reduce total body fat mass and increase satiety (assessed by hunger VAS as well as fat and total calorie intake at free buffet test meal).

Aim 2: To determine effects of GLP1RA on cardiometabolic risk factors. Secondary outcomes analysis: Secondary outcomes are change in the following metabolic CVD risk factors: blood glucose, triglycerides, HDL cholesterol, and hsCRP. All continuous secondary efficacy endpoints will be analyzed using similar repeated measures analyses to those previously described for the primary outcome to examine differences in the change in secondary outcomes, one at time, from baseline to 36 wk. Histograms will be examined, and if data are markedly skewed right, log transformations will be applied prior to analysis. Measures of insulin resistance and insulin secretion will be compared from baseline to 18 and 36 wk to test whether treatment effects are beneficial during the second half of intervention. Sample size and power: Table 3 shows observed relative effect sizes in our preliminary study for between treatment comparison of change from baseline to 3 mo (dataset from previous study[22]). Assuming a normal distribution of changes, a type I error rate of 0.05, and dropout rate of up to 20%, a sample size of 24 subjects per group (19 evaluable) will provide 85% power to detect relative treatment effect sizes of 1 or greater (in absolute value) for changes in cardiometabolic risk factors in patients with HO, which is consistent with the preliminary study.

Expected results and benchmarks for success (secondary efficacy endpoints): We expect that GLP1RA treatment will lead to improved metabolic CVD risk factors (higher HDL; lower blood pressure, blood glucose, hsCRP, and triglycerides).

Aim 3: To explore additional outcome measures, and predictors of treatment responses.
3a: Test GLP1RA treatment on energy homeostasis. Sample: All available EE and energy intake measures from DLW analyses and ASA24 dietary recalls at 0 and 36 wk will be included in the analyses (see Fig. 1). Tertiary outcomes analysis: The tertiary outcomes are change in EE and energy intake from baseline to 36 wk. Separate analyses will be conducted for EE and energy intake. For example for EE, an ANCOVA will be used to model the outcome of change in EE from baseline to 36 wk post-treatment with treatment as the factor of interest and Δ BMI and Δ energy intake included as covariates as both might affect EE independently of drug. A similar ANCOVA will be used to model the outcome of change in energy intake from baseline to 36 wk. Exploratory analyses will examine the change of energy intake after 6 and 18 wk of treatment to estimate effect sizes and inform the design of future studies.

Sample size and power: Assuming a normal distribution of differences, a type I error of 0.05, and a dropout rate of up to 20%, a final evaluable sample size of 19 subjects per group will provide 85% power to detect relative changes (average change divided by the pooled standard deviation (SD) of the change) in EE in relation to energy intake or energy intake in relation to EE of approximately 1 between the two groups. Based on preliminary pooled data from Ambler[114] and Eliakim[115] et al., the observed

pooled SDs of EE per DLW measures were 162 kcal/d and 155 kcal/d, respectively. Assuming a moderate correlation between baseline and follow-up measures (r=0.5), this would correspond to detectable differences of one pooled SD, or 162 kcal/d and 155 kcal/d, respectively. Expected results and benchmarks for success (exploratory efficacy endpoints): We expect that GLP1RA will lead to increased EE adjusted for Δ BMI and Δ energy intake.

3b: Determine predictors of GLP1RA treatment success. Sample: Pretreatment metabolic parameters and EE measures from DLW analyses (see Fig. 1), and all available outcomes measures will be included in the analyses (collected at 0 and 36 wk). Outcome measures and exploratory analyses: Potential predictors will be considered one at a time. Potential predictors include a hypothalamic lesion score; hyperphagia; EE; and the metabolic predictors leptin, adiponectin, sOB-R, α-MSH, HOMA-IR, WBISI including a leptin/Ob-R ratio.204 In addition to examining the relationship between the post-surgery lesion score (=standard approach for all subjects) and the response to GLP1RA treatment, we will perform a measurement study using high resolution images that would allow parcellation of the hypothalamus and surrounding areas. We expect that we will obtain images in the required high resolution quality in a subgroup of patients (50%; n=24). We will use these images for exploratory volumetric as well as topographic studies and will test if lesion volume or deficiencies in certain brain areas are associated with obesity outcomes or response to treatment using analyses similar to those described for lesion score. These exploratory measurement studies may be important for generating future hypotheses. A linear mixed-effects model will be fit with % change in BMI from baseline to follow-up as the outcome; treatment, time, the interaction between treatment and time, the potential predictor, and interactions between the potential predictor and treatment, time and treatment x time as factors of interest. Covariates and within-subject correlation matrix are as described for Specific Aim 1. Exploratory analyses will examine eating behavior and fat and total calorie intake as additional covariates. A contrast based on the interaction between the potential predictor and treatment x time will be used to estimate the direction and magnitude of the potential predictor on treatment response at 36 wk. Predictors will be standardized to be unitless, dividing by the SD to rank magnitudes and compare across predictors.

Sample size and power: For this exploratory aim no formal power calculations are conducted. Analyses will focus on the direction and magnitude of effects for use in planning future studies. Expected results and interpretation: We expect the degree of % change in BMI reduction (1) is positively associated with the degree of hyperphagia assessed by CEBQ, and (2) higher energy expenditure at baseline; (3) is negatively associated with insulin and leptin resistance as measured by WBISI, HOMA-IR, and leptin at baseline, and (4) is negatively associated with the post-operative hypothalamic lesion score (e.g., a higher score indicating greater hypothalamic damage).

5. SUBJECTS

Subjects

It is anticipated approximately 16 participants will be treated per year (5-6 per study site) during the first three years of the study. We expect to screen 80 subjects to get 48 subjects enrolled and 38 to complete the study (potential dropout rate of rate of 20%). Subjects will be between the ages of 10-25 y old at time of enrollment (11-27 y at end of intervention), and we expect each patient to complete the 56 week study.

Recruitment

We will recruit patients from the endocrinology clinics at the three sites, and will accept referrals from other endocrine providers. We will be advertising the study to other Pediatric Endocrinologists through a secure message board.

Enrollment

The PI at each site will screen and consent/assent subject or designate other qualified study staff to do so. Qualified participants will start with a 2-week placebo run-in to test adherence to the protocol. Immediately afterwards, subjects will be assigned treatment using a permuted-block randomization (1:1) with varying block sizes constructed by the Children's Core for Biomedical Statistics (CCBS) of Seattle Children's Research Institute (SCRI) stratified by study site, two age groups (10-14y, 15-25y), and gender. This is a double-blind study (participants and investigators both blinded). The study statistician will be blinded as well; a second statistician not involved in the conduct of the study will be responsible for the final preparation of the randomization scheme. Only the independent CCBS statistician and dispensing pharmacy at each site will know assigned study medications. It is anticipated approximately 16 participants will be treated per year (5-6 per study site) during the first three years of the study. We expect to screen 80 subjects to get 48 subjects enrolled and 38 to complete the study (potential dropout rate of rate of 20%). As we would expect many of these participants to be prepubertal as they have hypogonadotropic hypogonadism by virtue of their disease, pubertal status will not be used as an inclusion or exclusion criteria for the study.

Inclusion Criteria

- Age 10-25 years at time of enrollment
- Diagnosis of hypothalamic obesity with age- and sex adjusted BMI ≥ 95% or BMI ≥30 kg/m^2 if over 18 y
- History of craniopharyngioma or another tumor located in the hypothalamic area
- Hypothalamic lesion documented by neuroradiology
- ≥ 6 months post-surgical or radiation treatment
- Weight stable or increasing over 3 months prior to screening visit
- Stable hormone replacement for at least 3 months prior to screening visit

Exclusion Criteria

- Renal impairment (GFR<60 ml/min/1.73m^2 using the Schwarz formula[116])
- History of gastroparesis; pancreatitis or gallstones (unless status post cholecystectomy)
- Family history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma metabolic disorders
- Any insulin-treated diabetes mellitus, poorly controlled type 2 diabetes (HbA1c ≥ 10%), or any other chronic serious medical conditions such as CVD, malignancy or hematologic disorder, complicated syndromic disorder, or psychiatric disorders (schizophrenia, major depression, history of suicide attempts)
- Calcitonin >50 mg/L at screening
- Initiation of weight loss medications within 3 months of screening visit
- Previous donation of blood >10% of estimated blood volume within 3 months prior study
- Current warfarin use
- Current use of any other GLP1RA
- Untreated thyroid disorder or adrenal insufficiency

- History of bariatric surgery or planned bariatric surgery until end of study
- Pregnancy, lactation or expectation to conceive during study period
- Subject unlikely to adhere to study procedures in opinion of investigator
- Subject with contraindication to neuroimaging by MRI

6. STUDY PROCEDURES

For the placebo-controlled portion of the trial, each subject will have a screening visit and 4 study visits (weeks 0 [baseline], 6, 18, 36 [end of randomized trial]). Week 36 will also mark the beginning of the open label extension phase which will continue until week 54.

Screening Visit: The study will be explained to patients and their families and written consent/assent will be obtained. Medical history and concomitant medications will be documented. Vital signs will be recorded, including blood pressure, heart rate, respiratory rate and temperature. Body weight (lightly clothed) and height will be measured with a calibrated electronic scale and calibrated stadiometer. Hip and waist circumference measurements will be completed. A physical exam including Tanner staging will be done. This visit will also include:

- Blood draw for safety labs (electrolytes, CBC, lipase, amylase, glucose, transaminases (ALT, AST), creatinine, hemoglobin A1c, and thyroid hormones [TSH and free T4, or in patients with panhypopituitarism, free T4 only])
    - Blood for carcinoembryonic antigen (CEA) and calcitonin samples
- Blood for DNA extraction will be obtained for genetic markers (only at select sites)
- Urine pregnancy testing (HCG) will be done
- Instructions for 24h dietary recall.

Sexually active female participants are required to use birth control, unless they have documented gonadotropin deficiency.

Parents and participants (if appropriate) will be taught how to mix and inject the study medication. Parents/participants should perform a return demonstration before mixing the actual study medication. All teaching will be documented. Prior to leaving the clinic, parents/participants will inject the first dose of study medication under supervision. Dosing will be documented on the dosing log. Participants will be dispensed 1 more vial of study medication (placebo) to be administered at home the following week. The dose will be identical to the dosing provided in the blinded portion of the trial.

Study Visits (SVs): After the initial screening visit, there will be 5 study visits (see overview and measures in **Fig. 1**) to assess adherence, drug safety, outcomes, and to distribute the drug or placebo. Hypoglycemia medications will be adjusted as needed. During the duration of the treatment, subjects with persistent abdominal pain and nausea/vomiting will discontinue study medication and be evaluated for acute pancreatitis and cholecystitis. In children, most adverse effects are mild GI effects that are transient.[117] Subjects not tolerating their current dose will be discontinued from study at PI's discretion. Study medication will resume if and only if no significant adverse event is found and subjects concur. Subjects need to fast and refrain from exercise for ten hours prior to study visits for fasting blood draws. Physical exams including Tanner staging, and inspection of injection sites will be done at all visits (except no Tanner staging at 6 weeks visit). If a subject withdraws from the study or is withdrawn by an investigator for any reason, subjects will be asked to complete SV4 study procedures, not including the DEXA scan.

Other measures assessed at SVs (see Fig. 1):

- Questionnaires (eating, activity): SVs 1, 3, 4,
- 24h dietary recall-done the week prior to : SVs 1, 3, 4, 5
- Anthropometry: SVs 1, 2, 3, 4, 5
- Vital signs: SVs 1, 2, 3, 4, 5
- Actimetry: SVs 1, 3, 4
- Blood for metabolic outcomes: SVs 1, 3, 4, 5
- OGTT: SVs 1, 3, 4
- Energy intake at free buffet meal: SVs 1, 4
- Whole body DEXA in order to evaluate body composition: SVs 1, 4
- DLW energy balance assessment: SVs 1, 4
- ECGs: SVs 1, 3, 4, and 5
- Safety labs (electrolytes, CBC, lipase, amylase, glucose, ALT, AST, creatinine, hemoglobin A1c, and thyroid hormones): SVs 2, 3, 4, 5
    - Additional serum will be obtained at all sites and stored at a central location (SCRI Seattle) for future use (3 ml in case anti-exenatide antibodies will need to be assessed)
- CEA: SVs 3, 4, 5
- Calcitonin: SV 5
- MRI (if needed): SV 1

Weekly Contact: Research participants will be contacted weekly by telephone/email to assess for potential adverse events, concomitant medications, and compliance with dosing. Participants will also be reminded about their urine collections, diet recalls, and return of the accelerometer during these phone calls.

Visit Schedule:

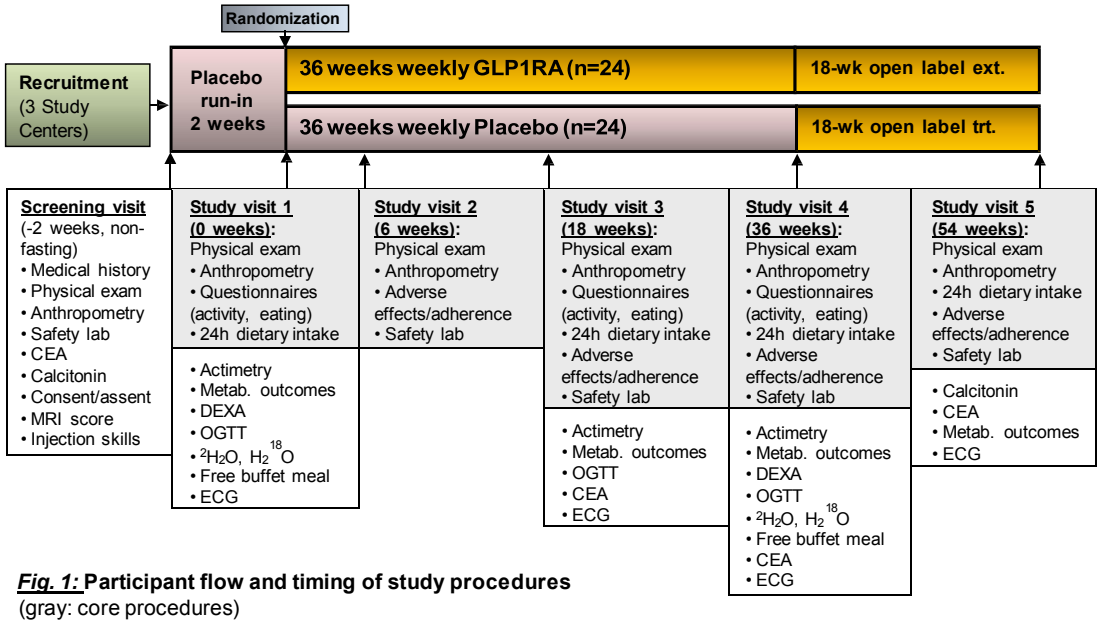

Fig. 1: **Participant flow and timing of study procedures**
(gray: core procedures)

7. RISKS/BENEFITS

Potential Risks
The subjects participating in this study will be exposed to physical, psychological, and financial risks. Participation in all aspects of the research will be voluntary. Subjects, their parents or their legal guardians will be advised that they can withdraw without penalty or refuse participation in any portion of the study at any time. Overall there are moderate risks to subjects. There is a risk of breach of patient confidentiality.

Potential risks to the participants enrolled in the study include:

1. Discomfort from hunger due to 10h fasting until 8:30 AM at four of the study visits (week 0, 18, 36, 54).

2. Pain, minor injury (bruising), nausea, infection or the development of a localized inflammation (thrombophlebitis) from placement of an intravenous catheter and obtaining serial blood samples. Rarely some people faint.

3. Loss of a small volume of blood (16-20 ml at the screening visit and week 54 visits; 9-13 ml at week 6 visit; and 32-36 ml per OGTT study visit at weeks 0, 18, and 36).

4. Patients will have a brain MRI if there was no recent MRI within 6 months prior to enrollment in the study. Potential risks from the MRI include anxiety, claustrophobic reactions or discomfort due to high noise, need to maintain a fixed posture, and/or interference between unidentified metal inside or outside the body and the scanner. The overall safety of MRI is well established. All MRI pulse sequences used are within FDA guidelines for time-varying magnetic fields. Additionally, echo-planar imaging (EPI) conveys the potential for damage to subjects' hearing as the EPI gradients produce noise in the 120 dB intensity range. Sound attenuating headphone

decrease the sound delivered by 40 dB, greatly reducing the intensity of the sound. Participants will be able to hear verbal commands given via the sound attenuating headphones that are at the volume level of conversational speech.

5. This research study involves exposure to very low dose radiation from two DEXA whole body scans. Each DEXA exposes the patient to the equivalent of less than one day of background radiation.

6. There is a slight risk of skin irritation during an ECG from the electrodes or gel that is used.

7. Participants may find it bothersome to answer the investigator's questions.

8. Discomfort, significant hyperglycemia, nausea, a reaction or sensitivity triggered by the oral dextrose solution. Discomfort, nausea, or a reaction from an unidentified food allergy or sensitivity to used study foods.

9. The DLW tracer is made up of the stable isotopes of hydrogen (^{2}H) and oxygen (^{18}O) and therefore does not gives out harmful radiation. These stable isotopes are found naturally in our drinking water and in our bodies. These isotopes have been used extensively to measure body composition and energy expenditure in premature infants, newborns, toddlers, children, adolescents, and pregnant and lactating women with no adverse effects. The deuterium oxide has been used across the world to measure human breast milk intakes in infants from newborns to 12 months of age. The DLW tracer in fact is cleaner than any tap water and fountain water.

10. Risks associated with the study drug. In this proposed study, subjects will receive weekly subcutaneous injections of placebo or ExQW 2 mg starting at week 0. ExQW may hurt an unborn child. It can change the way warfarin is metabolized. Exenatide is FDA approved for treatment of people with diabetes. Because the treatment in this study is investigational, there may be risks that we do not know about at this time.

    In a recent multicenter study including 461 adults with T2DM treated with ExQW for 26 weeks, 61% of patients had one or more adverse events (AEs).[31] Related to 461 patients, most frequent were injection site reactions (10% injection-site nodule, 4% subcutaneous nodule, 3% injection-site pruritus, 3% nodule, 2% injection-site erythema), followed by 9% developed nausea, 7% nasopharyngitis, 6% diarrhea, 6% headache, 5% decreased appetite, 5% constipation, 4% vomiting , 3% dizziness, 3% upper respiratory-tract infection, 3% abdominal pain, 2% dyspepsia, 2% unexpected therapeutic response, and 2% bronchitis. These results were similar to another clinical trial of adults with T2DM treated with ExQW up to 2 years.[37] Here 80% of subjects reported at least one AE, most frequently nausea (17%), injection site nodule (12%) and nasopharyngitis (12%). Overall expected AEs associated with the GLP-1 agonist ExQW may include:

Gastrointestinal AEs: The primary limiting factor for using GLP-1 agonists in humans has been gastrointestinal adverse events, in particular nausea, vomiting, diarrhea, and constipation, which occurred primarily during the first 6–8 weeks of therapy and declined thereafter. In the DURATION study trials the rates of gastrointestinal adverse events associated with ExQW treatment were for nausea 9.3-26.4%, diarrhea 6.1-18%, vomiting 3.7-11%, and constipation 4.6-10.8%.[34,109] For example, in a study of non-diabetic patients, 25% experienced nausea of mild to moderate severity.[118] The severity and incidence of nausea does decrease over time.

Pancreatic AEs: Controversial data exist regarding the risk for developing pancreatitis during treatment with GLP-1 agonists.[119,120] A recent integrated safety analysis from 19 completed randomized controlled trials, composite exposure-adjusted incidence rates for pancreatitis among exenatide twice daily users (n=3,261) and a pooled comparator group (n=2,333) were not statistically different.[121] However, the current package insert recommends that ExQW be discontinued immediately if pancreatitis is suspected.

Risk for hypoglycemia: In a 24-week monotherapy study of exenatide in subjects with type 2 diabetes, there was an approximately 5% incidence of minor hypoglycemia.[122] These episodes were all treated with oral glucose and subjects did not require any assistance from another person, glucagon or further medical attention. The addition of exenatide to metformin therapy does not increase the risk of hypoglycemia.[123] The overall reported rates for mild hypoglycemia were 0-5%; symptomatic hypoglycemia has not been seen in non-diabetic patients treated with exenatide.[118,124]

Thyroid AEs: In rodents, GLP-1 receptors are expressed on thyroid C-cells and administration of GLP-1 agonists can cause an increase in calcitonin levels and C-cell hyperplasia. [125,126] In human and primate tissue, however, few GLP-1 receptors are expressed on C-cells and GLP-1 agonists do not appear to increase calcitonin levels in vitro or in vivo.[127] Analysis of over 5,000 subjects treated with GLP-1 agonists and followed for up to 2 years did not reveal a pattern of calcitonin elevation or increased risk for C-cell hyperplasia or medullary thyroid carcinoma.[128] Although in humans there is no documentation of such a relationship, we will include calcitonin measures as safety measures.[128] Although Exenatide does not have an official FDA warning for medullary thyroid carcinoma, Bydureon has a boxed warning for the potential safety concern of thyroid C-cell tumors in animals (clinical correlate being MTC).

Kidney AEs: Exenatide is cleared by glomerular filtration. There have been post-marketing reports of altered renal function in patients taking exenatide. It is not clear whether the alteration in renal function is due to exenatide use, but the FDA recommends that exenatide not be used in patients with renal impairment.

Cardiovascular AEs: Exenatide may cause heart rate to increase by about 3 beats per minute. It is not known if this increase in heart rate causes any harm. In animal models, heart rate and blood pressure were increased by GLP-1 agonists. This effect was thought to be due to increased sympathetic tone.[129] In humans, however, numerous studies have demonstrated an improvement

in blood pressure with exenatide therapy.[109,122,130] In one 30 week trial of exenatide versus placebo, the between-group difference was a 4.4 mmHg reduction in systolic blood pressure and 3.4 mmHg in diastolic blood pressure for the exenatide group.[131] The same study did show a between-group difference in heart rate with a 3 beat per minute (95% CI, 0.8-5.2) increase in the exenatide group.[131] The clinical importance of the increased heart rate is unknown. The long term effects of exenatide on cardiovascular events are unknown. Change of QT interval was small and clinically insignificant. Intervention over periods of more than 6 months has shown small favorable effects on cardiovascular risk factors and biomarkers, i.e. reductions from baseline in systolic blood pressure, total cholesterol and low-density lipoprotein cholesterol (LDL), as well as triglycerides.

Endocrine AEs: A recent study[132] shows the GLP-1 receptor agonist Exendin-4 influences the gonadal axis, in both adult and prepubertal female rats. The effects of GLP-1 administration were on the hypothalamic Kiss-1 system, changed the amplitude of gonadotropin secretion, and influenced reproductive efficiency in female rats. This effect has not been reported in humans.

Allergic reactions and injection site reactions: Some people will have mild skin redness, itching or bruising at the site of medication injection.[31,38] Rarely, the medication can cause an allergic reaction. Antibody formation does occur with exenatide, as is expected with an injected amino acid.[133] The prevalence of antibody formation was 27-28%.[122] Antibody formation does not appear to decrease medication effectiveness.[123,134,135] There has been one case report of anaphylaxis to exenatide administration. The subject was treated with epinephrine and corticosteroids and exenatide was discontinued. Injection site reactions are mild, include redness, bruising or pruritus, and occur in up to 10% of subjects.[136]

11. Lastly, the financial risks associated with participating in this study are due to the potential of any health information being disclosed to health or life insurance companies or to current or potential employers. While this is a potentially serious risk, it is very unlikely, as we will keep all personally identifiable information physically separate from all health information. All information will be on password-protected computers, or in locked file cabinets in locked offices at the three study centers.

<u>Methods to Minimize Risks</u>

Risks will be minimized in a manner specific to each procedure referenced above. The risk to participants' privacy is minimal and every effort will be taken to maintain confidentiality. Risks to participants are minimized by screening and approaching only patients who qualify or have shown interest in being in the study via advertisements. The investigators of the three study sites are experienced in reviewing and obtaining consent and assent. All study procedures will be performed by staff experienced with such protocols and in pediatric research. The main risk is breach of patient confidentiality. However, this risk is minimized by keeping paper records in a locked office, and maintaining computerized records in the password protected REDCap database. Researchers are trained in HIPAA privacy regulations and other applicable privacy policies. No information will be released, nor will participation in the research be acknowledged, to any party except where compulsory according

to law or University policy. There may be unknown or unanticipated adverse effects from participation in this study for which the Principal Investigators and study team will remain observant.

Any unanticipated adverse events will be reported by the site PI's according to applicable IRB policy. The Principal Investigators are fully engaged in the actual performance of the study and this ensures that adverse events would be readily known and reported by the Principal Investigators. As per the Office for Human Research Protections (OHRP) guidelines, appropriate assent and parental consent will be obtained in this study.

Blood draws: The minimum amount of blood needed for assays will be drawn. Blood will be collected through phlebotomy (screening and visits at weeks 6 and 54) or a small intravenous line (visits at weeks 0, 18, and 36) after anesthetizing the skin with anesthetic cream. Blood draws during study visits at weeks 0, 18, and 36 (OGTT tests), require a total amount of 32-36 ml blood: 16-20 ml blood at baseline, and additionally, 4 blood draws of each 4 ml at 30, 60, 90, and 120 min after the oral glucose load. Lab parameters at the screening visit and study visit 5 (36 weeks) require each 16-20 ml blood, and 9-13 ml at study visit 2 (6 weeks). Total estimated amount of blood per subject equals to 137-161 ml or less during the whole 12-month study.

Hyperglycemia: The oral glucose load (1.75 g/kg, max. 75 g) can lead to significant hyperglycemia. All patients will be screened for diabetes before the study will be started. Any patient that meets the criteria for diabetes mellitus will be excluded from the OGTT and referred to the diabetes outpatient clinic for treatment. Any subject with insulin-treated diabetes mellitus or poorly controlled type 2 diabetes will be excluded from the study (see exclusion criteria). If patients develop diabetes during the study, management will be coordinated with their primary endocrinologist.

Nausea and abdominal discomfort: Due to the transient nature of the abdominal discomfort and nausea related to the study drug, and in order to prevent self-imposed drug holidays, all patients who experience nausea or abdominal discomfort are asked to contact the study team. The PI at each site will personally discuss appropriate therapy for this self-limited side effect.

Meals: At weeks 0, 18 and 36, subjects will have an OGTT (9:00-11:00 AM) in the fasting condition, which will be followed at weeks 0 and 36 by a standardized mixed meal caloric preload (macaroni & cheese at 11:00 AM) and a free buffet meal (at 12:30 PM). The test meal (macaroni & cheese) will be followed by an ad libitum buffet meal will be served consisting of a wide variety of food items and more than 100% of the subject's estimated daily calorie requirements. Children will have access to the buffet for 30 min., after which calorie intake and composition of consumed foods will be measured by weighing back uneaten food. Subjects will be screened for food allergies and sensitivities. In addition, all meals will be prepared fresh by the Clinical Research Center Nutrition Research Kitchen, and stored under adequate conditions. Duration of fasting is limited to 9:00 AM, and subjects can have water.

Neuroimaging: All subjects have had previous brain MRI scans before participation in this study. However, all subjects and their parents will be fully informed prior to beginning the study about the MRI procedure to reduce anxiety. Subjects in the MRI magnet will be able to talk to the experimenters at all times during the assessments, and are monitored by video. Should claustrophobia occur, subjects will be instructed that they can communicate to the MR technologist if they want to stop the scan. Subjects will have the option to discontinue the experiment at any time, and they will not be discouraged from doing so. There are planned procedures to minimize potential risks of metal

interference with the scanner by training the subjects and screening them properly before they go into the MRI scanning room. Subject safety requires that all ferrous materials be excluded from the immediate environment of the magnet. Hence, all subjects will be carefully checked prior to entering the magnet to make sure that no metallic objects remain on their person. Every subject will be screened for the presence of metallic objects. Any potential subject with contraindication to neuroimaging by MRI will be excluded from the study at the time of eligibility determination. Participants will be able to hear verbal commands given via the sound-attenuating headphones that are at the volume level of conversational speech. During MR scanning, the subjects will be monitored by video and audio. If any problems arise, the study will be terminated immediately. Additionally, the subjects will be given a call button that can be used at any time to stop the study.

The Principal Investigators will be accessible to answer questions and relieve anxiety whenever possible. Subjects, or their parents/legal guardians, may withdraw at any time or refuse to participate in all or part of any procedure without penalty. Subjects, or their parents/legal guardians, will have the option to discontinue the experiment at any time, and they will not be discouraged from doing so.

Potential Benefits

Individuals: The subjects will have a DEXA scan which provides information on their bone density and body composition. They will receive information about their metabolism, such as how many calories they burn per day. All subjects will receive the study medication during the second phase of the study. Subjects receiving Exenatide may experience weight loss.

Society: This research will test a promising drug intervention in the treatment of hypothalamic obesity. Furthermore, the proposed work will help us understand the biological mechanisms involved in the development of hypothalamic obesity. CP tumors are the *most common suprasellar tumors of nonglial origin* in children.[137] Severe obesity is a major risk factor for CP-related morbidity and mortality. The general public will benefit in a substantial way from an improved understanding of the etiology of obesity, and in particular of hypothalamic obesity, with the potential to lessen the burden on individual suffering as well as health care costs.

Adverse Events/Reporting

Investigator Oversight Responsibilities

Day-to-day oversight of the trial is provided by the Principal Investigators, Drs. Roth and Abuzzahab. Along with Dr. Ashley Shoemaker, Drs. Roth and Abuzzahab assure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the research plan approved by the three local IRBs (Seattle, St. Paul, Vanderbilt). Drs. Roth, Abuzzahab, and Shoemaker will review all study data, all adverse events (AEs), and any serious adverse events (SAEs) in real-time. All SAEs and dose-limiting toxicities will be reported to the independent Data Monitoring Committee (DMC) and IRB according to the approved Data and Safety Monitoring Plan.

External monitoring for the study is provided by the Institute of Translational Health Sciences (ITHS) of the University of Washington, and includes regular onsite data monitoring and regular review by the DMC (5 members), and the study team (i.e. Principal Investigators and co-investigator).

Monitoring Procedures
Please see details outlined separate Data and Safety Monitoring plan for adverse events monitoring and reviewing as well as DMC meetings and reporting for this study.

Adverse events are identified during study visits when potential AEs are assessed by clinical history and by physical examination of the subject. Each study site will report AEs to their IRBs as well according to their IRB guidelines. In addition, all AEs are reported according to Seattle Children's Hospital IRB reporting guidelines.

Serious adverse events and dose-limiting toxicities are submitted within one day of learning of the event to the IDMC via the REDCap SAE reporting system. Serious adverse events will be listed by organ system using the Medical Dictionary for Regulatory Activities (MedDRA) system. Study data and study conduct reports are prepared by the study statistician and include accrual, drop-outs, protocol deviations, and AEs in aggregate. These reports, including safety lab measures, SAEs and dose-limiting toxicities will be provided to the IDMC and the study team on a semi-annual basis for review.

Monitoring Reports
The DMC provides a written report to the study team with recommendations for study modification, study continuation/discontinuation as relevant. The study team is responsible for forwarding the report to the IRB.

Performance, Safety, and Treatment Issues
A report will be generated semi-annually by the study statistician and submitted to the DMC and study team. This report will include performance information including participant recruitment and retention, study conduct, data collection, quality control, and completion, and protocol adherence. This report will also include safety information, including any adverse events or dose-limiting toxicities. The report will also include results from treatment integrity/fidelity assessments to ensure the adequate and consistent provision of treatment.

Collection and Reporting of SAEs and AEs
For this study, the following standard AE definitions are used:

Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

Serious Adverse Event: Any AE that results in any of the following outcomes:
- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AE grading and attribution scale: As outlined in Data Safety and Monitoring Plan.

AE Management: See details in Data Safety and Monitoring Plan.

Emergency Unblinding. In case of drug-related SAEs and treatment-emergent adverse events (TEAEs) the Principal Investigators will be contacted immediately to contact the DMC (see data safety and monitoring plan) and consider the need to break the blind.

8. ADMINISTRATIVE PROCEDURES

Patient Confidentiality

A database will be designed for this study using REDCap (Research Electronic Data Capture) tools hosted at the Institute of Translational Health Sciences of which Seattle Children's and University of Washington are partners. REDCap is a secure, web-based application designed to support data capture for research studies, providing validated data entry, audit trails, seamless data downloads to common statistical packages, and mechanisms for importing data from external sources.[138] It will reside on a secure server with access provided exclusively to the research personnel. Access will be tailored for specific roles to maintain blinding. Subjects will be identified with a study identification number. A key to the subject identification number will be kept in a separate locked file drawer to which only the research coordinators have access. Reports will thereby be generated without PHI data and access will be restricted so that statisticians, etc. don't have access to all data.

Privacy and Confidentiality

Risk of leakage of PHI is minimized by keeping paper records in a locked cabinet and maintaining computerized records in the password protected REDCap data base. Researchers are trained in HIPAA privacy regulations. The study results will be kept for at least six years after the study is finished. The subjects consent to use or share PHI does not expire. If a subject changes their mind, we ask that they contact Drs. Christian Roth, Jennifer Abuzzahab, or Ashley Shoemaker in writing to withdraw consent.

Appendix: Checklists and questionnaires used in the study

Child Activity Checklist

This part of the survey is about your activities over the <u>past 7 days</u>, <u>not</u> including time you might spend doing these activities at school or work.

There are no right or wrong answers. No one does all these activities. Please be as accurate and honest as possible. For each activity listed, answer three questions:

1. ***Did you do this activity in the past 7 days? Circle yes or no.***
2. ***If yes, on how many days did you do the activity in the past 7 days?***
3. ***On average, how many minutes did you do the activity on the days that you did it?***

ACTIVITY	**No**	**Yes**	**How many days** in last 7 days?	On average, how many **minutes** did you do this activity **each day**?
Leisure Activity				
1. Computer /Internet	0	1	_____ days	_____minutes
2. Video games	0	1	_____ days	_____minutes
3. Homework, studying, work brought home	0	1	_____ days	_____minutes
4. Reading (not for school or work)	0	1	_____ days	_____minutes
5. Sitting and talking with friends (not on phone)	0	1	_____ days	_____minutes
6. Listening to music	0	1	_____ days	_____minutes
7. Talking on the phone	0	1	_____ days	_____minutes
8. Television or video watching	0	1	_____ days	_____minutes
9. Other (specify):	0	1	_____ days	_____minutes
10. Other (specify):	0	1	_____ days	_____minutes

Child Eating Behavior Questionnaire (CEBQ)

Please read the following statements and tick the boxes most appropriate to your child's eating behavior.

	Never	Rarely	Some times	Often	Always
My child loves food	□	□	□	□	□
My child eats more when worried	□	□	□	□	□
My child has a big appetite	□	□	□	□	□
My child finishes his/her meal quickly	□	□	□	□	□
My child is interested in food	□	□	□	□	□
My child is always asking for a drink	□	□	□	□	□
My child refuses new foods at first	□	□	□	□	□
My child eats slowly	□	□	□	□	□
My child eats less when angry	□	□	□	□	□
My child enjoys tasting new foods	□	□	□	□	□
My child eats less when s/he is tired	□	□	□	□	□
My child is always asking for food	□	□	□	□	□
My child eats more when annoyed	□	□	□	□	□
If allowed to, my child would eat too much	□	□	□	□	□
My child eats more when anxious	□	□	□	□	□
My child enjoys a wide variety of foods	□	□	□	□	□
My child leaves food on his/her plate at the end of a meal	□	□	□	□	□
My child takes more than 30 minutes to finish a meal	□	□	□	□	□

	Never	Rarely	Some times	Often	Always
Given the choice, my child would eat most of the time	□	□	□	□	□
My child looks forward to mealtimes	□	□	□	□	□
My child gets full before his/her meal is finished	□	□	□	□	□
My child enjoys eating	□	□	□	□	□
My child eats more when she is happy	□	□	□	□	□
My child is difficult to please with meals	□	□	□	□	□
My child eats less when upset	□	□	□	□	□
My child gets full up easily	□	□	□	□	□
My child eats more when s/he has nothing else to do	□	□	□	□	□
Even if my child is full up s/he finds room to eat his/her favorite food	□	□	□	□	□
If given the chance, my child would drink continuously throughout the day	□	□	□	□	□
My child cannot eat a meal if s/he has had a snack just before	□	□	□	□	□
If given the chance, my child would always be having a drink	□	□	□	□	□
My child is interested in tasting food s/he hasn't tasted before	□	□	□	□	□
My child decides that s/he doesn't like a food, even without tasting it	□	□	□	□	□
If given the chance, my child would always have food in his/her mouth	□	□	□	□	□
My child eats more and more slowly during the course of a meal	□	□	□	□	□

Adult Eating Behaviour Questionnaire

Please read each statement and tick the box most appropriate to you

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
I love food	☐	☐	☐	☐	☐
I often decide that I don't like a food, before tasting it	☐	☐	☐	☐	☐
I enjoy eating	☐	☐	☐	☐	☐
I look forward to mealtimes	☐	☐	☐	☐	☐
I eat more when I'm annoyed	☐	☐	☐	☐	☐
I often notice my stomach rumbling	☐	☐	☐	☐	☐
I refuse new foods at first	☐	☐	☐	☐	☐
I eat more when I'm worried	☐	☐	☐	☐	☐
If I miss a meal I get irritable	☐	☐	☐	☐	☐
I eat more when I'm upset	☐	☐	☐	☐	☐
I often leave food on my plate at the end of a meal	☐	☐	☐	☐	☐
I enjoy tasting new foods	☐	☐	☐	☐	☐
I often feel hungry when I am with someone who is eating	☐	☐	☐	☐	☐
I often finish my meals quickly	☐	☐	☐	☐	☐
I eat less when I'm worried	☐	☐	☐	☐	☐
I eat more when I´m anxious	☐	☐	☐	☐	☐
Given the choice, I would eat most of the time	☐	☐	☐	☐	☐

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
I eat less when I'm angry	☐	☐	☐	☐	☐
I am interested in tasting new food I haven't tasted before	☐	☐	☐	☐	☐
I eat less when I'm upset	☐	☐	☐	☐	☐
I eat more when I'm angry	☐	☐	☐	☐	☐
I am always thinking about food	☐	☐	☐	☐	☐
I often get full before my meal is finished	☐	☐	☐	☐	☐
I enjoy a wide variety of foods	☐	☐	☐	☐	☐
I am often last at finishing a meal	☐	☐	☐	☐	☐
I eat more and more slowly during the course of a meal	☐	☐	☐	☐	☐
I eat less when I'm annoyed	☐	☐	☐	☐	☐
I often feel so hungry that I have to eat something right away	☐	☐	☐	☐	☐
I eat slowly	☐	☐	☐	☐	☐
I cannot eat a meal if I have had a snack just before	☐	☐	☐	☐	☐
I get full up easily	☐	☐	☐	☐	☐
I often feel hungry	☐	☐	☐	☐	☐
When I see or smell food that I like, it makes me want to eat	☐	☐	☐	☐	☐
If my meals are delayed I get light-headed	☐	☐	☐	☐	☐
I eat less when I'm anxious	☐	☐	☐	☐	☐

Hyperphagia Questionnaire

(1) How upset does your child generally become when denied a desired food?

___Not particularly upset at all
___A little upset
___Somewhat upset
___Very upset
___Extremely upset

(2) How often does your child try to bargain or manipulate to get more food at meals?

___A few times a year
___A few times a month
___A few times a week
___Several times a week
___Several times a day

(3) Once your child has food on their mind, how easy is it for you or others to re-direct your child away from food to other things?

___Extremely easy, takes minimal effort to do so
___Very easy, takes just a little effort to do so
___Somewhat hard, takes some effort to do so
___Very hard, takes a lot of work to do so
___Extremely hard, takes sustained and hard work to do so

(4) How often does your child forage through the trash for food?

___Never
___A few times a year
___1–2 times a month
___1–3 times a week
___4 to 7 times a week

(5) How often does your child get up at night to food seek?

___Never
___A few nights a year
___1–2 nights a month
___1–3 nights a week
___4 to 7 nights a week

(6) How persistent is your child in asking or looking for food after being told “no” or “no more”?

___Lets go of food ideas quickly and easily
___Lets go of food ideas pretty quickly and easily
___Somewhat persistent with food ideas
___Very persistent with food ideas
___Extremely persistent with food ideas

(7) Outside of normal meal times, how much time does your child spend talking about food or engaged in food-related
behaviors?

___Less than 15 minutes a day
___15 to 30 minutes a day
___30 minutes to an hour
___1 to 3 hours a day
___more than 3 hours a day

(7) How often does your child try to steal food (that you are aware of?)

___A few times a year
___A few times a month
___A few times a week
___Several times a week
___Several times a day

(8) When others try to stop your child from talking about food or engaging in food-related behaviors, it generally leads to:

___No distress or upset
___Mild distress or upset
___Moderate distress or upset
___Severe distress or upset
_ Extreme distress, behaviors can’t usually be stopped

(9) How clever or fast is your child in obtaining food?

___Not particularly clever or fast
___A little clever or fast
___Somewhat clever or fast
___Very clever or fast
___Extremely clever of fast

(11) To what extent to food-related thoughts, talk, or behavior interfere with your child's normal daily routines, self-care,
school, or work?

___No interference
___Mild interference; occasional food-related interference in completing school, work, or hygiene task
___Moderate interference; frequent food-related interference in completing school, work, or hygiene tasks
___Severe interference; almost daily food-related interference in completing school, work, or hygiene tasks
___Extreme interference, often unable to participate in hygiene tasks or to get to school or work due to food-related difficulties

References

1. Muller HL. Childhood craniopharyngioma. Recent advances in diagnosis, treatment and follow-up. Horm Res 2008;69:193-202.
2. Muller HL, Emser A, Faldum A, et al. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. J Clin Endocrinol Metab 2004;89:3298-305.
3. Ostrom QT, Gittleman H, Farah P, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. Neuro Oncol 2013;15 Suppl 2:ii1-56.
4. Srinivasan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT. Features of the metabolic syndrome after childhood craniopharyngioma. J Clin Endocrinol Metab 2004;89:81-6.
5. Simoneau-Roy J, O'Gorman C, Pencharz P, Adeli K, Daneman D, Hamilton J. Insulin sensitivity and secretion in children and adolescents with hypothalamic obesity following treatment for craniopharyngioma. Clin Endocrinol (Oxf) 2010;72:364-70.
6. Mong S, Pomeroy SL, Cecchin F, Juraszek A, Alexander ME. Cardiac risk after craniopharyngioma therapy. Pediatr Neurol 2008;38:256-60.
7. Erfurth EM. Endocrine aspects and sequel in patients with craniopharyngioma. J Pediatr Endocrinol Metab 2015;28:19-26.
8. Olsson DS, Andersson E, Bryngelsson IL, Nilsson AG, Johannsson G. Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in sweden. J Clin Endocrinol Metab 2015;100:467-74.
9. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature 2006;444:875-80.
10. Greenway FL, Bray GA. Treatment of hypothalamic obesity with caffeine and ephedrine. Endocr Pract 2008;14:697-703.
11. Hamilton JK, Conwell LS, Syme C, Ahmet A, Jeffery A, Daneman D. Hypothalamic Obesity following Craniopharyngioma Surgery: Results of a Pilot Trial of Combined Diazoxide and Metformin Therapy. Int J Pediatr Endocrinol 2011;2011:417949.
12. Bereket A, Kiess W, Lustig RH, et al. Hypothalamic obesity in children. Obes Rev 2012;13:780-98.
13. Lustig RH. Hypothalamic obesity after craniopharyngioma: mechanisms, diagnosis, and treatment. Front Endocrinol (Lausanne) 2011;2:60.
14. Lustig RH. Hypothalamic obesity: causes, consequences, treatment. Pediatr Endocrinol Rev 2008;6:220-7.
15. Lustig RH, Hinds PS, Ringwald-Smith K, et al. Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2003;88:2586-92.
16. Danielsson P, Janson A, Norgren S, Marcus C. Impact sibutramine therapy in children with hypothalamic obesity or obesity with aggravating syndromes. J Clin Endocrinol Metab 2007;92:4101-6.
17. Mason PW, Krawiecki N, Meacham LR. The use of dextroamphetamine to treat obesity and hyperphagia in children treated for craniopharyngioma. Arch Pediatr Adolesc Med 2002;156:887-92.
18. Ismail D, O'Connell MA, Zacharin MR. Dexamphetamine use for management of obesity and hypersomnolence following hypothalamic injury. J Pediatr Endocrinol Metab 2006;19:129-34.
19. Roth CL. Hypothalamic obesity in patients with craniopharyngioma: profound changes of several weight regulatory circuits. Front Endocrinol (Lausanne) 2011;2:49.
20. Elfers CT, Simmons JH, Roth CL. Glucagon-like peptide-1 agonist exendin-4 leads to reduction of weight and caloric intake in a rat model of hypothalamic obesity. Horm Res Paediatr 2012;78:47-53.

21. Simmons JH, Shoemaker AH, Roth CL. Treatment with glucagon-like Peptide-1 agonist exendin-4 in a patient with hypothalamic obesity secondary to intracranial tumor. Horm Res Paediatr 2012;78:54-8.
22. 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;167:355-60.
23. Ottney A. Glucagon-like peptide-1 receptor agonists for weight loss in adult patients without diabetes. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 2013;70:2097-103.
24. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest 2014;124:4473-88.
25. Bloom S, Wynne K, Chaudhri O. Gut feeling--the secret of satiety? Clin Med 2005;5:147-52.
26. 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;11:RA271-8.
27. Gutzwiller JP, Degen L, Heuss L, Beglinger C. Glucagon-like peptide 1 (GLP-1) and eating. Physiology & behavior 2004;82:17-9.
28. Ma X, Bruning J, Ashcroft FM. Glucagon-like peptide 1 stimulates hypothalamic proopiomelanocortin neurons. J Neurosci 2007;27:7125-9.
29. Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012;344:d7771.
30. Gedulin BR, Nikoulina SE, Smith PA, et al. Exenatide (exendin-4) improves insulin sensitivity and {beta}-cell mass in insulin-resistant obese fa/fa Zucker rats independent of glycemia and body weight. Endocrinology 2005;146:2069-76.
31. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013;381:117-24.
32. Aroda VR, Ratner R. The safety and tolerability of GLP-1 receptor agonists in the treatment of type 2 diabetes: a review. Diabetes Metab Res Rev 2011;27:528-42.
33. Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared with exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. Ann Pharmacother 2011;45:850-60.
34. Stolar MW, Grimm M, Chen S. Comparison of extended release GLP-1 receptor agonist therapy versus sitagliptin in the management of type 2 diabetes. Diabetes Metab Syndr Obes 2013;6:435-44.
35. Senda M, Ogawa S, Nako K, Okamura M, Sakamoto T, Ito S. The glucagon-like peptide-1 analog liraglutide suppresses ghrelin and controls diabetes in a patient with Prader-Willi syndrome. Endocr J 2012;59:889-94.
36. Linnebjerg H, Kothare PA, Skrivanek Z, et al. Exenatide: effect of injection time on postprandial glucose in patients with Type 2 diabetes. Diabet Med 2006;23:240-5.
37. Norwood P, Liutkus JF, Haber H, Pintilei E, Boardman MK, Trautmann ME. Safety of exenatide once weekly in patients with type 2 diabetes mellitus treated with a thiazolidinedione alone or in combination with metformin for 2 years. Clin Ther 2012;34:2082-90.
38. Inagaki N, Atsumi Y, Oura T, Saito H, Imaoka T. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. Clin Ther 2012;34:1892-908 e1.

39. Jensterle M, Kocjan T, Kravos NA, Pfeifer M, Janez A. Short-term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome. Endocr Res 2014:1-6.
40. Jensterle Sever M, Kocjan T, Pfeifer M, Kravos NA, Janez A. Short-term combined treatment with liraglutide and metformin leads to significant weight loss in obese women with polycystic ovary syndrome and previous poor response to metformin. Eur J Endocrinol 2014;170:451-9.
41. Feng P, Yu DM, Chen LM, et al. Liraglutide reduces the body weight and waist circumference in Chinese overweight and obese type 2 diabetic patients. Acta pharmacologica Sinica 2015;36:200-8.
42. Shao Y, Yuan G, Feng Y, Zhang J, Guo X. Early liraglutide treatment is better in glucose control, beta-cell function improvement and mass preservation in db/db mice. Peptides 2014;52:134-42.
43. Russo GT, Labate AM, Giandalia A, et al. Twelve-month treatment with Liraglutide ameliorates Visceral Adiposity Index and common cardiovascular risk factors in type 2 diabetes outpatients. J Endocrinol Invest 2014.
44. Inoue K, Maeda N, Fujishima Y, et al. Long-term impact of liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, on body weight and glycemic control in Japanese type 2 diabetes: an observational study. Diabetol Metab Syndr 2014;6:95.
45. Iglesias P, Civantos S, Vega B, Pavon I, Guijarro G, Monereo S. Clinical Effectiveness of Exenatide in Diabetic Patients Waiting for Bariatric Surgery. Obes Surg 2015.
46. Flint A, Raben A, Ersboll AK, Holst JJ, Astrup A. The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. Int J Obes Relat Metab Disord 2001;25:781-92.
47. Bradley DP, Kulstad R, Racine N, Shenker Y, Meredith M, Schoeller DA. Alterations in energy balance following exenatide administration. Appl Physiol Nutr Metab 2012;37:893-9.
48. Pannacciulli N, Bunt JC, Koska J, Bogardus C, Krakoff J. Higher fasting plasma concentrations of glucagon-like peptide 1 are associated with higher resting energy expenditure and fat oxidation rates in humans. Am J Clin Nutr 2006;84:556-60.
49. Flint A, Raben A, Rehfeld JF, Holst JJ, Astrup A. The effect of glucagon-like peptide-1 on energy expenditure and substrate metabolism in humans. Int J Obes Relat Metab Disord 2000;24:288-98.
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;20:364-70.
51. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114:555-76.
52. Flynn JT, Mitsnefes M, Pierce C, et al. Blood pressure in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children study. Hypertension 2008;52:631-7.
53. Cohen M, Syme C, McCrindle BW, Hamilton J. Autonomic nervous system balance in children and adolescents with craniopharyngioma and hypothalamic obesity. Eur J Endocrinol 2013;168:845-52.
54. Harz KJ, Muller HL, Waldeck E, Pudel V, Roth C. Obesity in patients with craniopharyngioma: assessment of food intake and movement counts indicating physical activity. J Clin Endocrinol Metab 2003;88:5227-31.
55. Holmer H, Pozarek G, Wirfalt E, et al. Reduced energy expenditure and impaired feeding-related signals but not high energy intake reinforces hypothalamic obesity in adults with childhood onset craniopharyngioma. J Clin Endocrinol Metab 2010;95:5395-402.
56. Kim RJ, Shah R, Tershakovec AM, et al. Energy expenditure in obesity associated with craniopharyngioma. Childs Nerv Syst 2010;26:913-7.
57. Butte NF, Wong WW, Adolph AL, Puyau MR, Vohra FA, Zakeri IF. Validation of cross-sectional time series and multivariate adaptive regression splines models for the prediction of energy expenditure in children and adolescents using doubly labeled water. J Nutr 2010;140:1516-23.

58. Schoeller DA. Validation of habitual energy intake. Public Health Nutr 2002;5:883-8.
59. Treuth MS, Butte NF, Wong WW. Effects of familial predisposition to obesity on energy expenditure in multiethnic prepubertal girls. Am J Clin Nutr 2000;71:893-900.
60. Roberts SB, Coward WA, Ewing G, Savage J, Cole TJ, Lucas A. Effect of weaning on accuracy of doubly labeled water method in infants. Am J Physiol 1988;254:R622-7.
61. Butte NF, Wong WW, Ferlic L, Smith EO, Klein PD, Garza C. Energy expenditure and deposition of breast-fed and formula-fed infants during early infancy. Pediatr Res 1990;28:631-40.
62. Schulz LO, Schoeller DA. A compilation of total daily energy expenditures and body weights in healthy adults. Am J Clin Nutr 1994;60:676-81.
63. Casper RC, Schoeller DA, Kushner R, Hnilicka J, Gold ST. Total daily energy expenditure and activity level in anorexia nervosa. Am J Clin Nutr 1991;53:1143-50.
64. Schoeller DA, Levitsky LL, Bandini LG, Dietz WW, Walczak A. Energy expenditure and body composition in Prader-Willi syndrome. Metabolism 1988;37:115-20.
65. Motil KJ, Schultz RJ, Wong WW, Glaze DG. Increased energy expenditure associated with repetitive involuntary movement does not contribute to growth failure in girls with Rett syndrome. J Pediatr 1998;132:228-33.
66. Welk GJ, Corbin CB, Dale D. Measure issues in the assessment of physical activity in children. Research Quarterly for Exercise and Sport 2000;71:59-73.
67. Trost SG, Ward DS, Moorehead SM, Watson PD, Riner W, Burke JR. Validity of the computer science and applications (CSA) activity monitor in children. Medicine and Science in Sports and Exercise 1998;30:629-33.
68. Janz KF. Validation of the CSA accelerometer for assessing children's physical activity. Medicine and Science in Sports and Exercise 1994;26:369-75.
69. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Medicine and Science in Sports and Exercise 1998;30:777-81.
70. Trost SG, Pate RR, Freedson PS, Sallis JF, Taylor WC. Using objective physical activity measures with youth: How many days of monitoring are needed? Medicine and Science in Sports and Exercise 2000;32:426-31.
71. Trost SG, Pate RR, Sallis JF, et al. Age and gender differences in objectively measured physical activity in youth. Medicine and Science in Sports and Exercise 2002;34:350-5.
72. Trost SG, Loprinzi PD, Moore R, Pfeiffer KA. Comparison of Accelerometer Cut-points for Predicting Activity Intensity in Youth. Med Sci Sports Exerc 2010.
73. Sallis JF, Strikmiller PK, Harsha DW, et al. Validation of interviewer- and self-administered physical activity checklists for fifth grade students. Med Sci Sports Exerc 1996;28:840-51.
74. Sallis JF, Saelens BE. Assessment of physical activity by self-report: status, limitations, and future directions. Res Q Exerc Sport 2000;71:S1-14.
75. Garcia AW, George TR, Coviak C, Antonakos C, Pender NJ. Development of the child/adolescent activity log: a comprehensive and feasible measure of leisure-time physical activity. Int J Behav Med 1997;4:323-38.
76. Wardle J, Guthrie CA, Sanderson S, Rapoport L. Development of the Children's Eating Behaviour Questionnaire. J Child Psychol Psychiatry 2001;42:963-70.
77. Dykens EM, Maxwell MA, Pantino E, Kossler R, Roof E. Assessment of hyperphagia in Prader-Willi syndrome. Obesity (Silver Spring) 2007;15:1816-26.
78. Sherafat-Kazemzadeh R, Ivey L, Kahn SR, et al. Hyperphagia among patients with Bardet-Biedl syndrome. Pediatr Obes 2013;8:e64-7.

79. Shoemaker AH, Cone RD. Drinking and eating behaviors in children with pseudohypoparathyroidism type 1a Poster presentation at the 95th meeting of the Endocrine Society, San Francisco, CA, 6/2013 2013.
80. Han JC, Liu QR, Jones M, et al. Brain-derived neurotrophic factor and obesity in the WAGR syndrome. N Engl J Med 2008;359:918-27.
81. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr 1990;51:241-7.
82. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985;39 Suppl 1:5-41.
83. 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;24:38-48.
84. Shields BJ, Palermo TM, Powers JD, Grewe SD, Smith GA. Predictors of a child's ability to use a visual analogue scale. Child Care Health Dev 2003;29:281-90.
85. Roth CL, Aylward E, Liang O, Kleinhans NM, Pauley G, Schur EA. Functional Neuroimaging in Craniopharyngioma: A Useful Tool to Better Understand Hypothalamic Obesity? Obes Facts 2012;5:243-53.
86. Myers MG, Jr., Heymsfield SB, Haft C, et al. Challenges and opportunities of defining clinical leptin resistance. Cell Metab 2012;15:150-6.
87. Reinehr T, Kratzsch J, Kiess W, Andler W. Circulating soluble leptin receptor, leptin, and insulin resistance before and after weight loss in obese children. Int J Obes (Lond) 2005;29:1230-5.
88. Roth CL, Enriori PJ, Gebhardt U, et al. Changes of peripheral alpha-melanocyte-stimulating hormone in childhood obesity. Metabolism 2010;59:186-94.
89. Considine RV. Increased serum leptin indicates leptin resistance in obesity. Clin Chem 2011;57:1461-2.
90. Yoon JH, Park JK, Oh SS, et al. The ratio of serum leptin to adiponectin provides adjunctive information to the risk of metabolic syndrome beyond the homeostasis model assessment insulin resistance: the Korean Genomic Rural Cohort Study. Clin Chim Acta 2011;412:2199-205.
91. Yun JE, Won S, Mok Y, Cui W, Kimm H, Jee SH. Association of the leptin to high-molecular-weight adiponectin ratio with metabolic syndrome. Endocr J 2011;58:807-15.
92. Karakas M, Zierer A, Herder C, et al. Leptin, adiponectin, their ratio and risk of Coronary Heart Disease: results from the MONICA/KORA Augsburg Study 1984-2002. Atherosclerosis 2010;209:220-5.
93. Diamond FB, Jr., Cuthbertson D, Hanna S, Eichler D. Correlates of adiponectin and the leptin/adiponectin ratio in obese and non-obese children. J Pediatr Endocrinol Metab 2004;17:1069-75.
94. 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;28:902-9.
95. Yeckel CW, Taksali SE, Dziura J, et al. The normal glucose tolerance continuum in obese youth: evidence for impairment in beta-cell function independent of insulin resistance. J Clin Endocrinol Metab 2005;90:747-54.
96. Yeckel CW, Weiss R, Dziura J, et al. Validation of insulin sensitivity indices from oral glucose tolerance test parameters in obese children and adolescents. J Clin Endocrinol Metab 2004;89:1096-101.
97. Stumvoll M, Mitrakou A, Pimenta W, et al. Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. Diabetes Care 2000;23:295-301.
98. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462-70.

99. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
100. Makris N, Swaab DF, van der Kouwe A, et al. Volumetric parcellation methodology of the human hypothalamus in neuroimaging: normative data and sex differences. Neuroimage 2013;69:1-10.
101. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage 2006;31:1116-28.
102. Friedman SD, Ishak GE, Poliachik SL, et al. Callosal alterations in pyridoxine-dependent epilepsy. Dev Med Child Neurol 2014;56:1106-10.
103. Mai JK, Paxinos G, Voss T. Atlas of the human brain. ACADEMIC PRESS 1997.
104. 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;37:1443-51.
105. Petri KC, Jacobsen LV, Klein DJ. Comparable Liraglutide Pharmacokinetics in Pediatric and Adult Populations with Type 2 Diabetes: A Population Pharmacokinetic Analysis. Clinical pharmacokinetics 2015.
106. Aroda VR, Henry RR, Han J, et al. Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: meta-analysis and systematic review. Clin Ther 2012;34:1247-58 e22.
107. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39-47.
108. Bradley DP, Kulstad R, Schoeller DA. Exenatide and weight loss. Nutrition 2010;26:243-9.
109. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 2008;372:1240-50.
110. Ridge T, Moretto T, Macconell L, et al. Comparison of safety and tolerability with continuous (exenatide once weekly) or intermittent (exenatide twice daily) GLP-1 receptor agonism in patients with type 2 diabetes. Diabetes Obes Metab 2012.
111. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. Wiley: Hoboken, NJ 2004.
112. Dunton GF, Liao Y, Intille SS, Spruijt-Metz D, Pentz M. Investigating children's physical activity and sedentary behavior using ecological momentary assessment with mobile phones. Obesity (Silver Spring) 2011;19:1205-12.
113. Trost SG, Loprinzi PD, Moore R, Pfeiffer KA. Comparison of accelerometer cut points for predicting activity intensity in youth. Med Sci Sports Exerc 2011;43:1360-8.
114. Ambler C, Eliakim A, Brasel JA, Lee WN, Burke G, Cooper DM. Fitness and the effect of exercise training on the dietary intake of healthy adolescents. Int J Obes Relat Metab Disord 1998;22:354-62.
115. Eliakim A, Brasel JA, Mohan S, Wong WL, Cooper DM. Increased physical activity and the growth hormone-IGF-I axis in adolescent males. Am J Physiol 1998;275:R308-14.
116. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629-37.
117. Boland CL, Harris JB, Harris KB. Pharmacological Management of Obesity in Pediatric Patients. Ann Pharmacother 2015;49:220-32.
118. Rosenstock J, Klaff LJ, Schwartz S, et al. Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without pre-diabetes. Diabetes Care 2010;33:1173-5.

119. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology 2011;141:150-6.
120. Raschi E, Piccinni C, Poluzzi E, Marchesini G, De Ponti F. The association of pancreatitis with antidiabetic drug use: gaining insight through the FDA pharmacovigilance database. Acta Diabetol 2013;50:569-77.
121. Macconell L, Brown C, Gurney K, Han J. Safety and tolerability of exenatide twice daily in patients with type 2 diabetes: integrated analysis of 5594 patients from 19 placebo-controlled and comparator-controlled clinical trials. Diabetes Metab Syndr Obes 2012;5:29-41.
122. Moretto TJ, Milton DR, Ridge TD, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2008;30:1448-60.
123. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005;28:1092-100.
124. Khoo EY, Wallis J, Tsintzas K, Macdonald IA, Mansell P. Effects of exenatide on circulating glucose, insulin, glucagon, cortisol and catecholamines in healthy volunteers during exercise. Diabetologia 2010;53:139-43.
125. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology 2010;151:1473-86.
126. Vangoitsenhoven R, Mathieu C, Van der Schueren B. GLP1 and cancer: friend or foe? Endocr Relat Cancer 2012;19:F77-88.
127. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology 2010;151:1473-86.
128. Hegedus L, Moses AC, Zdravkovic M, Le Thi T, Daniels GH. GLP-1 and calcitonin concentration in humans: lack of evidence of calcitonin release from sequential screening in over 5000 subjects with type 2 diabetes or nondiabetic obese subjects treated with the human GLP-1 analog, liraglutide. J Clin Endocrinol Metab 2011;96:853-60.
129. Yamamoto H, Lee CE, Marcus JN, et al. Glucagon-like peptide-1 receptor stimulation increases blood pressure and heart rate and activates autonomic regulatory neurons. J Clin Invest 2002;110:43-52.
130. Tokuda M, Katsuno T, Ochi F, et al. Effects of exenatide on metabolic parameters/control in obese Japanese patients with type 2 diabetes. Endocr J 2014;61:365-72.
131. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med 2011;154:103-12.
132. Outeirino-Iglesias V, Romani-Perez M, Gonzalez-Matias LC, Vigo E, Mallo F. GLP-1 increases pre-ovulatory LH source and the number of mature follicles, as well as synchronizing the onset of puberty in female rats. Endocrinology 2015:en20141978.
133. Jespersen MJ, Knop FK, Christensen M. GLP-1 agonists for type 2 diabetes: pharmacokinetic and toxicological considerations. Expert Opin Drug Metab Toxicol 2013;9:17-29.
134. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004;27:2628-35.
135. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care 2005;28:1083-91.

136. Blevins T, Pullman J, Malloy J, et al. DURATION-5: Exenatide Once Weekly Resulted in Greater Improvements in Glycemic Control Compared with Exenatide Twice Daily in Patients with Type 2 Diabetes. J Clin Endocrinol Metab 2011;96:1301-10.
137. Harwood-Nash DC. Neuroimaging of childhood craniopharyngioma. Pediatr Neurosurg 1994;21 Suppl 1:2-10.
138. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.