Protocol Title	Role of Pharmacotherapy in Counteracting Weight Regain in Adolescents with Severe Obesity
Principal Investigator	Name: Aaron S Kelly, PhD
	Department: Pediatrics; Center for Pediatric Obesity Medicine
	Telephone Number: (612) 626-3492
	Email Address: kelly105@umn.edu
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IND/IDE Holder	Aaron Kelly, Ph.D.
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PROTOCOL COVER PAGE

ANCILLARY REVIEWS

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☒ **Yes** ☐ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See guidance on next page.	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☒ **Yes** ☐ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups each have their own application process.**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu Contact:*	
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	

☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☒ **Yes** ☐ **No**	Use data from the Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: ics@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: cdrifka@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact: kmmccorm@umn.edu*	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	2.0	This protocol amendment adds the following items: • Adds a 400-meter walk test at four timepoints during the study; • Allows for test results to be shared with the parent upon request; • Adds a heart rate measurement at the Screening visit. This protocol amendment revises the following items: • Notes that the safety labs at the Screening visit do not need to be repeated if the Baseline visit occurs within 30 days of the Screening visit; • Revises the statistical section; • Revises the exclusion criteria; • Allows sexually active females to now be on one form of contraception; • Revises the Recruitment section; • Revises the Compensation section. This protocol amendment removes the ambulatory blood pressure monitoring in a subset of participants.	Yes
2	3.0	Based on feedback from the FDA this protocol amendment asks that participants who are sexually active to utilize two forms of contraception. Monthly urine pregnancy tests will be required from females of childbearing potential. Test kits will be supplied for conducting these at home for the timepoints where there is no planned in-person visit. Amendment also includes increasing the meal replacement phase daily calorie count to 1,200 kcals and provision of a modest monetary incentive for completing the monthly lifestyle modification counseling sessions.	Yes
3	4.0	Revises the schedule of events and description of visits to note the activities that will take place on a monthly basis via telephone.	Yes
4	5.0	Makes revisions to the protocol based on suggestions from the FDA. These changes include asking participants who can get pregnant to correctly and consistently utilize	Yes

Revision #	Version Date	Summary of Changes	Consent Change?
		two forms of contraception and documenting this at all visits (in person and telephone). Revises the protocol so that adverse events are collected starting at the Randomization visit. To review concomitant medications at all visits. To clarify that discontinuation of Qsymia for any reason should include a tapering regimen. To add heart rate collection at all study visits. We are also adding in payments to families for dropping off the urine samples 7 days after the baseline, randomization, week 26 and week 52 visits for those participants who are randomized to receive the doubly labeled water for energy expenditure tests. Changes the Week 8 visit to be an in-person visit so that dose titration of the study medication can occur. Changes the IND holder of the record to Aaron Kelly.	
5	6.0	Updated the footnotes of the schedule of events	No
6	7.0	Removes the arterial stiffness and heart rate variability testing from the project. Expands the recruitment to send out letters to individuals who are on the waiting list to be seen in the Pediatric Weight Management Clinic.	Yes
7	8.0	Provides safety clarifications regarding contraception and PHQ-9 questionnaire cutoffs. Provides a Greenphire Clincard to parents who attend long visits (Screening, Baseline, Week 25 or Week 52) to help offset the cost of a meal.	Yes
8	9.0	Corrects the protocol to match the currently approved parental consent form, adult consent form and assent forms.	No
9	10.0	Study drug supply chain issues have been encountered. This protocol revision will develop a plan for tapering doses if supply chain issues are not resolved in 3-6 months. It also adds the risk of seizure information to the protocol.	No
10	11.0	Revises the total compensation section.	Yes
11	12.0	Adds the Minneapolis YWCA as a community partnership to section 10.0 of the protocol.	No
12	13.0	Revises who can conduct Tanner staging	No
13	14.0	Adds a hemoglobin A1c to be done at screening. Updates the schedule of events and section 7.2 of the protocol.	Yes

Revision #	Version Date	Summary of Changes	Consent Change?
14	15.0	Updates the schedule of events to note that study drug (for the down titration) will be dispensed at the Week 52 visit	Yes
15	16.0	Revises section 3.1 of the protocol to note that participants will be asked to strictly follow the eating regimen, which will include a total of approximately 1,200 kcals per day of commercially-available liquid shakes, pre-packaged frozen entrée meals, two servings of fruit, and three servings of vegetables. Updates section3.1 for individuals who attend a school where no public microwave is available and offers a letter to be able to utilize a microwave.	No
16	17.0	Makes clarifications to the study exclusion criteria.	No
17	18.0	Notes that Qsymia is now approved for use in adolescents by the FDA.	Yes
18	19.0	Revises section 4.2 and 17.0 of the protocol to align with the new IRB guidance regarding suicide risk.	Yes
19	20.0	Makes revisions to the protocol based on an HRPP audit. Revises sections 6.2 and 16.1 of the protocol to note that the analysis of samples conducted by a Fairview lab will be posted to the participant's medical record and results from other laboratory analyses will not be shared. Clarifies the study exclusion criteria (section 7.1 of the protocol) surrounding seizure disorders. Revises the schedule of events to individually list tests that are to be performed to avoid staff confusion and updates the visit detail (this was not brought up by the HRPP audit team).	Yes
20	21.0	Revises section 4.2 and 12.0 of the protocol do clarify when comprehensive metabolic panels will be undertaken so that they match the schedule of events in the protocol. Adds to section 4.2 that additional tests may be done if a safety issue is suspected. We are also revising the enrollment goal to about 100 individuals who consent, complete the screening visit, complete the baseline visit and start the meal replacement therapy portion of the project.	Yes
21	22.0	Revises section 1.1 of the protocol to review the history of the review and approval of the study drug by the FDA during the course of this project.	Yes

Revision #	Version Date	Summary of Changes	Consent Change?
22	23.0	Removes use of the BRIEF from the schedule of events, and protocol sections 4.2, 7.2 and 12.1 of the protocol. Update section 12.1 of the protocol with regard to the instance of rash (seen in < 2% of patients).	Yes

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ABBREVIATIONS/DEFINITIONS

ACE-Q Teen	Adverse Childhood Experiences Questionnaire-Teen
ADHD	Attention Deficit Hyperactivity Disorder
AEBQ	Adult Eating Behavior Questionnaire
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
A-V	Atrioventricular
BMI	Body Mass Index
CANTAB	Cambridge Neuropsychological Test Automated Battery
CEBQ	Child Eating Behavior Questionnaire
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CPT-II	Connors Continuous Performance Test II
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTSI	Clinical and Translational Science Institute
DBP	Diastolic Blood Pressure
DEBQ	Dutch Eating Behavior Questionnaire
DHEAS	Dehydroepiandrosterone
DSMB	Data and Safety Monitoring Board
DXA	Dual-Energy X-ray Absorptiometry
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
HDL	High-Density Lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
IDS	Investigational Drug Service
iDXA	Intelligent Dual-Energy X-ray Absorptiometry
IRB	Institutional Review Board
ITT	Intent to Treat
IWQOL-Kids	Impact of Weight on Quality of Life-Kids
LDL	Low-Density Lipoprotein
LH	Luteinizing Hormone
MPH	Mental Health Professional
MN-POC	Minnesota Pediatric Obesity Consortium
mSv	Millisievert
NIDDK	National Institute of Diabetes and Digestive Kidney Diseases
NIH	National Institutes of Health
PAQ-A	Physical Activity Questionnaire for Adolescents
PedsQL	Peds Quality of Life Questionnaire
PHQ-9	Patient Health Questionnaire
PP	Per protocol
pQCT	Peripheral Quantitative Computed Tomography
QEWP-A	Questionnaire on Eating and Weight Patterns
RED-5	Reward Based Eating Drive Scale
SBP	Systolic Blood Pressure
SOC	Standard of Care
TSH	Thyroid Stimulating Hormone
UPIRTSO	Unanticipated Problem Involving Risk to Subjects or Others
U.S.	United States
VO2-max	The maximum volume of oxygen consumed by the body each minute during exercise while breathing air at sea level

1.0 Objectives

1.1 Purpose:

Long-term weight loss maintenance is seldom achieved by individuals with obesity owing to numerous biological adaptations occurring in the post-weight loss setting, including neuroendocrine-mediated changes in appetite/satiety and reduction of energy expenditure. Following weight loss, peripheral and central mechanisms respond in a way similar to starvation by conveying a sense that energy reserves have dwindled, activating a strong counter-response to increase caloric intake. Moreover, metabolic rate drops, further compounding the propensity for weight rebound. Adolescents with severe obesity are not immune to the vexing issue of weight regain; therefore, effective and scalable treatments are urgently needed. Pharmacotherapy has the potential to prevent weight regain by targeting counter-regulatory mechanisms in the post-weight loss setting. The combination of phentermine and topiramate was approved by the US FDA for the treatment of obesity in children 12 and older on 27Jun2022. However, this study was enrolling participants before that approval and its use was considered experimental. For participants who enrolled in the study after 27Jun2022, this research falls within the approved parameters for use. The mechanisms of action are thought to reduce appetite, enhance satiety, and potentially increase energy expenditure, making this medication particularly well-suited for the purpose of weight loss maintenance since it targets many of the biological adaptations known to induce relapse and subsequent weight regain. Our group has generated preliminary data demonstrating that both phentermine and topiramate reduce BMI in adolescents with severe obesity and have acceptable safety profiles. In this clinical trial, we will utilize combination phentermine/topiramate to target counter-regulatory pathways responsible for weight regain after meal replacement therapy (structured meals of known caloric content) in adolescents with severe obesity with a goal of enhancing weight loss maintenance and improving obesity-related complications. Importantly, we will maximize the clinical utility and overall impact of our study by comprehensively characterizing the safety of phentermine/topiramate (cognition and bone health) as well as examine the extent to which this medication counteracts mechanisms of weight regain.

2.0 Background

2.1 Significance of Research Question/Purpose:

Severe obesity, afflicting ~8% of adolescents in the U.S., is a serious and challenging medical and public health problem.[1,2] The number and levels of cardiovascular risk factors are considerably higher in the context of severe obesity compared to milder forms of obesity.[3] Approximately 85% of youth with severe obesity have ≥1 cardiovascular risk factor.[4] Non-alcoholic fatty liver disease is highly-prevalent among adolescents with severe obesity with estimates nearing 60%.[5] Subclinical atherosclerosis and arterial stiffening is present in youth with severe obesity at levels similar to those with type 2 diabetes.[6] Youth with severe obesity have high levels of inflammation and oxidative stress,[7] adverse adipokine profiles,[8] and arterial endothelial activation.[9] Moreover, longitudinal data implicate obesity in childhood as a strong predictor of future risk factor clustering and sub-clinical atherosclerosis in adulthood.[10-12] Risk of developing type 2 diabetes is high in youth with severe obesity.[13-15] Severe obesity in adolescence is associated with chronic disability from a wide range of causes later in life.[16] Perhaps most disturbing is the poor long-term prognosis for these youth. Approximately 90% will have a BMI ≥35 kg/m^2 in adulthood.[4] Disturbingly, severe obesity in adulthood reduces life expectancy by 7-14 years.[17]

In the field of obesity management, weight loss maintenance has proven to be an arduous challenge. Indeed, long-term weight loss maintenance is seldom achieved owing to numerous biological adaptations occurring in the post-weight loss setting. These include, but are not limited to, neuroendocrine changes in the gut-brain axis influencing appetite and satiety and reduction of energy expenditure.[18-20] Following weight loss, peripheral and central mechanisms respond in a way similar to starvation by conveying a sense that energy reserves have dwindled, activating a strong and persistent counter-response to increase caloric intake.[19] Moreover, metabolic rate decreases, further compounding the propensity for weight rebound.[18] These counter-regulatory adaptations persist for many years following initial weight loss, and in fact might be permanent.[20,21]

Adolescents with severe obesity (BMI ≥120% above the 95th percentile or BMI ≥35 kg/m^2) are not immune to the vexing issue of weight regain as evidenced by the poor outcomes of interventions using lifestyle modification alone.[22-25] Indeed, large clinic-based studies from Europe and the U.S. reported that only a small fraction of patients were able to achieve and maintain clinically-meaningful weight loss with lifestyle modification

therapy.[22,26] Metabolic/bariatric surgery is an effective treatment[27] but uptake is very low[28] and many pediatricians and parents are concerned about the irreversible nature of this treatment and worry about the possibility of long-term (decades) risks, which are currently unknown. Therefore, a large treatment gap exists between lifestyle modification therapy and metabolic/bariatric surgery that remains unfilled.

Pharmacotherapy has the potential to prevent weight regain by targeting counter-regulatory mechanisms in the post-weight loss setting, with various agents demonstrating improved long-term weight loss durability in adults.[29-32] Until recently, orlistat was the only FDA-approved anti-obesity medication for adolescents but it is rarely prescribed because of modest efficacy and notable side effects.[33] The combination of phentermine and topiramate is an attractive option owing to its relatively high degree of efficacy compared to other medications.[32] The combination of phentermine/placebo (under the name Qsymia) was approved in June 2022 for adolescents, after our study had been started. Placebo-subtracted weight loss at one and two years with phentermine/topiramate is 9% at the top dose in adult trials.[34-36] The mechanisms of action of phentermine/topiramate, which together are thought to reduce appetite, enhance satiety, and potentially increase energy expenditure, are well-suited for the purpose of weight loss maintenance since they target many of the biological adaptations known to induce relapse and subsequent regain. [18-20]

The rationale for specifically focusing on phentermine/topiramate (vs. other medications) to prevent weight regain is supported by its multiple mechanisms of action, which are thought to target many of the post-weight loss counter-regulatory biological adaptations known to induce relapse. These mechanisms include: 1) reducing appetite through inhibition of norepinephrine reuptake (phentermine) and reduction of hypothalamic glutamate neurotransmission (topiramate) and lowering the levels of neuropeptide Y (topiramate); 2) enhancing satiety by slowing gastric emptying (combination of phentermine/topiramate); and 3) increasing energy expenditure (both phentermine and topiramate independently).[37-43] Through these mechanisms of action, sustained weight loss has been demonstrated with phentermine/topiramate treatment in adults.[44] While other obesity medications target some of these pathways, their respective mechanisms of action are generally less comprehensive, and accordingly have lower efficacy, ranging from 3-5% placebo-subtracted weight reduction at 1 year.[45]

In terms of safety, topiramate is FDA-approved in children and adolescents for the treatment of seizures and migraine headaches with a reasonable safety track-record. Importantly, we observed no signal of cognitive problems in a pilot clinical trial of topiramate for the treatment of obesity. Phentermine is FDA-approved for short-term use in ages >16 years old for treatment of obesity and is the most widely-prescribed adult obesity medication in the U.S.[46] And, the combination of phentermine/topiramate was recently FDA-approved for the treatment of adolescent obesity. Although in a distinct medication class, phentermine is not dissimilar in mechanism of action and side effects to many of the stimulant medications widely-prescribed for the treatment of ADHD in youth. Adult data suggest no adverse cardiovascular effects or increased risk of addiction potential or withdrawal symptoms associated with phentermine use,[47,48] and our clinical experience with phentermine in adolescents with obesity demonstrated an acceptable safety profile.[49]

2.2 Preliminary Data:

We present preliminary data demonstrating that phentermine and topiramate reduce BMI as respective monotherapies and to a greater degree in combination, and have acceptable safety profiles. Moreover, we and others have shown that although meal replacement therapy (structured meals of known caloric content) can elicit robust short-term weight loss (6% BMI reduction over a few months) in adolescents with severe obesity, weight regain is a pervasive problem.[50] Therefore, in this clinical trial, we propose to combine these interventions in a chronological fashion and utilize phentermine/topiramate to target counter-regulatory pathways thought to be responsible for weight regain following meal replacement therapy in youth with severe obesity. Participants achieving ≥5% BMI reduction with short-term (six weeks) use of meal replacements will be randomized (1:1) to phentermine/topiramate or placebo for an additional 52 weeks while simultaneously engaging in lifestyle modification therapy. Based on adult outcomes with phentermine/topiramate[36, 44] and expected weight regain in the placebo group,[50] we anticipate a mean placebo-subtracted BMI reduction of 8-10% at 52 weeks, a level considered clinically-meaningful in adolescents.[51]

Importantly, this study will also allow us to further investigate the safety of phentermine/topiramate. We will perform in-depth and extensive physiological assessments to provide pediatricians with the information they need to make a balanced judgement of the benefits/risks of phentermine/topiramate treatment for obesity. The safety-related

rationale for combination pharmacotherapy is that lower doses of the individual constituent medications can be used, which might minimize side effects. However, to our knowledge, no combination medications have yet been tested in the pediatric population in a randomized, placebo-controlled safety/efficacy trial.

Lastly, we have aimed to maximize the impact of our trial by characterizing the mechanisms of action of phentermine/topiramate, uniquely in the context of weight loss maintenance, to begin to uncover clues about the types of patients most likely to benefit from treatment. Visual analog scales and standardized eating behavior questionnaires will allow us to track and quantify changes in appetite and satiety. Serial assessment of resting metabolic rate (via indirect calorimetry) and total energy expenditure (via doubly-labeled water in a subset of participants) will elucidate the degree to which phentermine/topiramate offsets the counterproductive increase in energy efficiency often observed in the context of weight loss. Although hypothesis-generating, results will provide a framework for the design of future studies with targeted hypotheses addressing response prediction. For example, we may find that patients reporting high levels of appetite and poor satiety at baseline respond the most favorably to treatment and/or those with the largest initial decrease in resting metabolic rate and/or total energy expenditure benefit most in regard to weight loss maintenance. Indeed, precision medicine has been identified by the NIH as a high priority area for adolescent severe obesity.[52]

Short-Term Weight Loss with Meal Replacements in Adolescents with Severe Obesity

Meal replacement therapy is an effective short-term treatment for obesity. Meta-analyses of adult obesity studies have shown that meal replacements reduce body weight to a greater extent than conventional diets.[53,54] The rationale for the use of meal replacements is that individuals with obesity, particularly adolescents,[55] often underestimate caloric intake; adherence to a strict, predetermined meal regimen removes the “guesswork” from eating. Berkowitz et al.[50] demonstrated promising short-term weight loss efficacy (BMI reduction of ~6%) in adolescents with severe obesity using meal replacements for a period of four months. Despite the positive short-term effectiveness, weight regain ensued in most participants.[50] Therefore, meal replacement therapy appears to be an effective “kick-start” for weight loss; however, longer-term outcomes could likely be enhanced with subsequent treatments that mitigate the counter-regulatory biological adaptations favoring weight regain (i.e., a tool offering individuals a fighting chance to keep the weight off). We conducted an unpublished clinical trial in

adolescents with severe obesity that included a two-month meal replacement induction period. Out of 39 participants, 28 (72%) successfully achieved a 5% BMI reduction benchmark. These results provide evidence of the success of short-term meal replacement therapy in our hands and offer guidance for the design of the proposed clinical trial (we anticipate approximately 70% will achieve the 5% BMI reduction goal).

Table 1 (below) summarizes the mean changes in BMI, body fat percentage, select cardiometabolic risk factors, resting metabolic rate, and liver fat (expressed as hepatic fat fraction) in participants who were able to reduce their BMI by ≥5% during the meal replacement phase of our above-mentioned unpublished study (and on whom we had complete follow-up data, N=26). Again, our goal in the currently-proposed trial is to evaluate the utility of pharmacotherapy in targeting the counter-regulatory pathways responsible for weight regain in an effort to "hold the line" on weight loss (and improvements in obesity related complications) and ideally further enhance it after short-term meal replacement therapy. In other words, we want to sustain and further enhance these benefits.

Table 1. Mean Changes in BMI, Body Fat, Cardiometabolic Risk Factors, and Metabolic Rate

Sample Size	Measure	Baseline (SD)	Post-MR (SD)	% change	p-value (paired t-test)
n=26	**BMI (kg/m^2)**	40.1 (4.0)	37.9 (3.9)	-5.6	<0.001
n=26	**Body Fat (%)**	48.9 (4.3)	47.9 (5.0)	-2.1	<0.001
n=26	**SBP (mmHg)**	121 (9)	118 (9)	-2.7	0.032
n=26	**TG (mg/dL)**	106 (56)	92 (34)	-12.6	0.04
n=26	**HDL (mg/dL)**	40 (7)	39 (21)	-1.1	0.909
n=26	**Insulin (uU/mL)**	15 (10)	10 (5)	-33.8	0.02
n=26	**RMR (kcal/day)**	2059 (365)	1939 (355)	-5.9	0.006
n=10	**HFF (%)**	11.3 (8.1)	8.3 (7.1)	-27.0	0.027

Abbreviations: BMI = Body mass index; SBP = Systolic blood pressure; TG = Triglyceride; HDL= High-density lipoprotein cholesterol; RMR = Resting metabolic rate; HFF = hepatic fat fraction

Existing Literature:

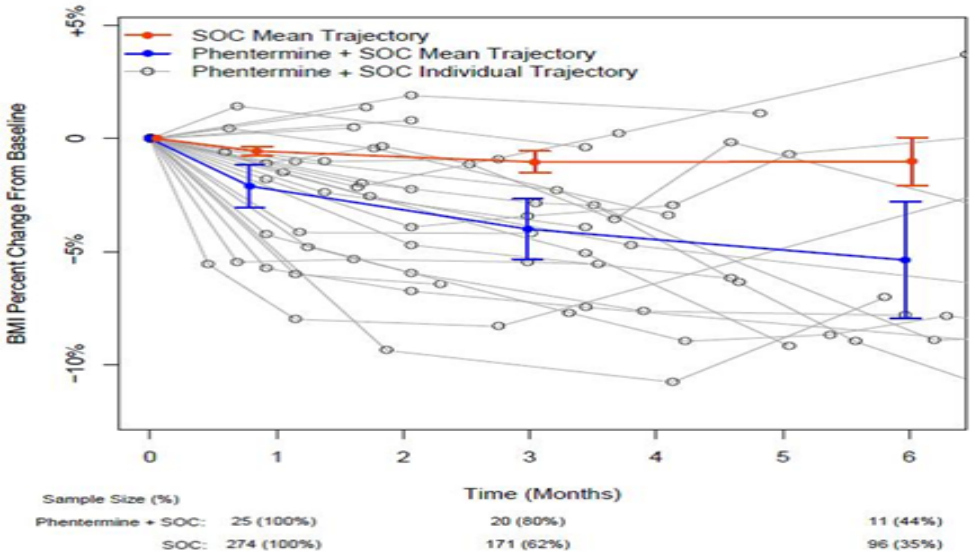
Systematic Clinical Experience with Phentermine Monotherapy in Adolescents with Severe Obesity

In this published retrospective study, we reported on the change in BMI and adverse events among adolescents engaging in lifestyle modification therapy only (standard of care: SOC) and phentermine monotherapy + SOC in our pediatric weight management program where standard protocols for phentermine treatment have been implemented.[49]

We identified 25 patients (mean age 16.1±1.3 years; mean BMI 41.2±6.9 kg/m^2) prescribed phentermine (15 mg/day) + SOC and a comparison group of 274 patients matched on age and BMI receiving only SOC. Phentermine treatment was associated with a greater percent change in BMI at one month (-1.6% [95% CI (-2.6%, -0.6%); p=0.001), three months (-2.9% [95% CI (-4.5%, -1.4%); p<0.001]) and six months (-4.1% [95% CI (-7.1%, -1.0%); p=0.009]). At three months, 40% of the phentermine group achieved ≥5% BMI reduction vs. 8.8% in the SOC group; at 6 months, this increased to 63.6% of the phentermine group vs. 20.8% in the SOC group.

Since publishing this paper, we have updated the analysis with additional patients and have slightly expanded the window of follow-up at the six-month time-point. We identified 29 patients (mean age 15.8±1.6 years; mean BMI 40.7±7.1 kg/m^2) prescribed phentermine (15 mg/day) + SOC and a comparison group of 920 patients matched on age and BMI receiving only SOC. Phentermine treatment was associated with a greater percent change in BMI at one month (-1.7% [95% CI (-2.6%, -0.8%); p<0.001), three months (-2.9% [95% CI (-4.1%, -1.7%); p<0.001]) and six months (-3.5% [95% CI (-5.8%, -1.2%); p=0.004]). At three months, 36% of the phentermine group achieved ≥5% BMI reduction vs. 3.6% in the SOC group; at six months, this increased to 57.9% of the phentermine group vs. 6.8% in the SOC group. Importantly, there were no statistically- or clinically-significant differences in systolic or diastolic blood pressure in the phentermine group. Moreover, adult data suggest no increased risk of addiction potential or withdrawal symptoms associated with phentermine use.[5]

Figure 1. Change in BMI with Phentermine vs. Standard of Care



Systematic Clinical Experience with Topiramate Monotherapy in Adolescents with Severe Obesity

In this retrospective study, we reported on the change in BMI and adverse events among adolescents prescribed topiramate monotherapy (according to our standardized clinical protocol) and lifestyle modification therapy in our pediatric weight management program.[56] Twenty-eight patients (mean age 15.2 ± 2.5 years; mean baseline BMI 46.2 ± 10.3 kg/m^2) who were prescribed doses of topiramate ranging from 75 to 100 mg daily, were included in the analysis. The six-month percent change in BMI was −4.9, [95% confidence interval (−7.1, −2.8), P < 0.001]. At six months, 50% of the patients experienced at least 5% reduction in BMI from baseline. Intermittent paresthesia (tingling in the extremities) was reported in 2/28 (7%). No other adverse events/side effects were reported (including no reports of cognitive dulling). These preliminary results suggest that topiramate is associated with clinically-meaningful BMI reduction with a reasonable and acceptable safety profile.

A Pilot, Randomized, Placebo-Controlled Trial of Topiramate for Weight Loss Maintenance

We conducted a randomized, placebo-controlled pilot clinical trial evaluating the preliminary efficacy and safety of topiramate following short-term meal replacement therapy in adolescents with severe obesity.[57] Participants completed four weeks of meal replacement therapy followed by 24 weeks of treatment with either topiramate 75 mg/day or placebo. Thirty adolescents (mean age 15.2 ± 1.7 years, mean BMI 40.3 ± 4.6 kg/m^2) completed the meal replacement phase and were randomized; 21 completed the study. The difference in mean percent change in BMI between the topiramate and placebo groups did not reach statistical significance (-1.9% [95% CI (-5.2%, +1.5%); P=0.291]). We learned from this trial that the dose of topiramate used (75 mg/day) was probably too low and that monotherapy may be insufficient in this population – ultimately setting the stage for our plans to evaluate topiramate at a higher dose (92 mg/day) and in combination with phentermine (15 mg/day).

Importantly, our primary areas of focus in this pilot trial were safety, tolerability, and acceptability. We employed a comprehensive panel of questionnaires and computer-based tests pre and post including: Cambridge Neuropsychological Test Automated Battery (CANTAB) (a computerized test of motor speed, memory, and attention), and the Connors Continuous Performance Test II (CPT II) (a computerized measure of attention and impulsivity). Bone density and geometry were assessed with peripheral quantitative computed tomography (pQCT) and DXA.

The most common adverse event was paresthesia (tingling in the extremities), reported by 25% in the topiramate group and none in the placebo group. Table 2 summarizes the neurocognitive safety results. There were no statistically- or clinically-significant differences between the topiramate and placebo group on any of the CANTAB subscales. For the CPT II, only the hit reaction time was different indicating a faster reaction time in the topiramate group compared with placebo. No statistically- or clinically-significant changes in bone health were observed. None of the participants withdrew due to experiencing adverse events.[57]

Table 2. Change in Neurocognitive-Related Safety Variables from Randomization to 24 Weeks

Outcome	*N*	Placebo Δ, mean (SD)	Topiramate Δ, mean (SD)	Mean difference, topiramate-placebo (95% CI)	*P*
CANTAB					
Standard PAL	21	−0.24 (0.23)	0.04 (0.60)	0.26 (−0.16 to 0.69)	0.238
Standard PAL shapes	21	−0.24 (0.53)	0.11 (1.62)	0.07 (−0.74 to 0.88)	0.863
Standard PRM	21	0.24 (0.80)	−0.64 (2.00)	−0.70 (−2.13 to 0.73)	0.348
Standard SSP	19	0.11 (0.79)	0.36 (1.21)	0.16 (−0.80 to 1.11)	0.750
CPT II					
Omissions %	20	−0.09 (18.09)	0.34 (4.62)	−3.81 (−13.72 to 6.09)	0.461
Commissions %	20	2.20 (7.29)	1.55 (11.04)	−0.30 (−8.01 to 7.42)	0.941
Hit reaction time	20	6.37 (10.38)	−2.67 (7.44)	−11.13 (−18.32 to −3.93)	0.008
BRIEF-SR					
BRI T-score	15	1.17 (10.96)	−1.00 (8.80)	−1.97 (−10.57 to 6.62)	0.661
MI T-score	14	0.33 (13.38)	0.00 (5.32)	−0.64 (−10.50 to 9.21)	0.900
GEC T-score	14	1.00 (12.81)	−1.00 (7.52)	−2.02 (−11.74 to 7.71)	0.692

BRI, behavior regulation index; CANTAB, Cambridge Neuropsychological Test Automated Battery; CPT II, Connors Continuous Performance Test II; BRIEF-SR, Behavior Rating Inventory of Executive Function-Self Report; GEC, global executive composite; MI, metacognition index; PAL, paired associates learning; PRM, pattern recognition memory; SSP, spatial span.

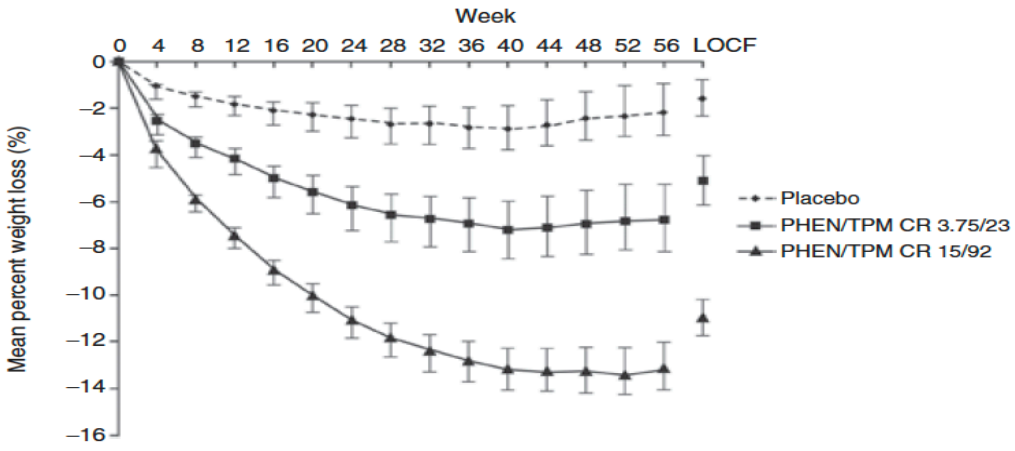
These preliminary data suggest that the side effect profile of topiramate is acceptable in adolescents. Although the treatment effect was relatively modest, as shown below we expect superior efficacy with combination therapy as demonstrated in adults, with additive benefit when phentermine is co-administered.

Treatment Effect of Phentermine/Topiramate in Adults

Phentermine/topiramate was approved by the FDA in 2012 for the treatment of obesity in adults. This orally-administered medication is available in mid- (phentermine 7.5 mg; topiramate 46 mg) and high- (phentermine 15 mg; topiramate 92 mg) doses, administered once per day. In a meta-analysis, phentermine/topiramate was shown to be the most effective obesity medication currently available.[34] A large dose-ranging trial in adults evaluating phentermine and topiramate as monotherapies vs. phentermine/topiramate demonstrated superior efficacy of the combination with an acceptable safety profile.[58]

Results from a large phase III clinical trial demonstrated placebo-subtracted weight loss of >9% with treatment for one year at the top dose.[18] Importantly, a separate trial demonstrated that the treatment effect is durable out to at least two years.[35] The most common side effects in these trials were paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth. Improvements were noted in blood pressure, lipids, glucose, insulin, HOMA-IR, C-reactive protein, and adiponectin.

Figure 2. Percent Body Weight Loss with Phentermine/Topiramate in Adults with Severe Obesity



Systematic Clinical Experience with Phentermine/Topiramate Combination Therapy in Adolescents with Severe Obesity: Preliminary Safety, Tolerability, and Acceptability (unpublished data)

We performed a chart review of patients treated with phentermine and topiramate within our pediatric weight management clinic. Our healthcare providers carefully and systematically assess and document adverse events with obesity pharmacotherapy at all follow-up visits according to established protocols. We identified 55 patients (37 females/18 males) ages 11-20 years old (mean age 15.4±2.3 years) with a baseline mean BMI of 43.2±10.2 kg/m^2. The most commonly-prescribed doses were 15 mg/day of phentermine and 75-100 mg/day of topiramate. The mean duration of combination treatment was 11.1±10.3 months. Owing to variability regarding how these medications were prescribed in the clinic, we do not report on changes in BMI. In other words, many patients were started on either phentermine or topiramate monotherapy followed by the addition of the other medication at a later time-point. Table 3 summarizes: 1) the incidence of the most

commonly-reported adverse events; 2) the percent of patients experiencing resolution of the adverse event(s) while remaining on treatment; and 3) the percent of patients that discontinued treatment as a result of the adverse event(s). Overall, results demonstrated a low incidence of adverse events with a relatively high rate of resolution. Importantly, only a small percentage of the patients discontinued therapy as a result of adverse events. Therefore, these results provide preliminary evidence supporting the safety of these medications and demonstrate a reasonably high level of acceptability and tolerability in the adolescent population.

Table 3. Adverse Events, Resolution, and Acceptability of Phentermine/Topiramate Treatment

Adverse Event Description	Overall Percent Affected	Percent Resolution (of those affected)	Overall Percent Discontinued Owing to Adverse Event
Jittery/Shaky	3.6%	100%	0%
Moody/Irritable	10.9%	83%	1.8%
Difficulty Sleeping	1.8%	100%	0%
Dizziness	1.8%	100%	0%
Headache	3.6%	50%	1.8%
Paresthesia	10.9%	100%	0%
Cognitive Dulling	5.4%	66.7%	1.8%
Tachycardia	1.8%	0%	1.8%

Preliminary Safety and Efficacy of Phentermine/Topiramate in Adolescents with Obesity (unpublished data)

The manufacturer of phentermine/topiramate recently completed a pharmacokinetic trial among adolescents (12-17 years old) with obesity (BMI ≥95th percentile) and shared the results with our group. Here we report on participants that were randomized to either placebo (N=14; 9 females) or high-dose phentermine/topiramate (15 mg/92 mg) (N=13; 9 females) and received treatment for 56-days. In brief, pharmacokinetic results were similar to adults. In aggregate, adverse events were experienced by 50% of the placebo group and 77% of the phentermine/topiramate group. Details of the adverse events are shown in Table 4.

Table 4. Adverse Events of Phentermine/Topiramate Treatment in Adolescents with Obesity

Adverse Event Description	Placebo Group (%)	Phentermine/Topiramate Group (%)
Dry Mouth	0%	8%
Abdominal Pain	0%	0%
Constipation	0%	0%
Diarrhea	0%	0%
Ear Infection	0%	0%
Nasopharyngitis	7%	0%
Pharyngitis	0%	0%
Procedural Pain	7.1%	0%
Urine Osmolarity Increase	0%	0%
Back Pain	0%	0%
Headache	21%	15%
Paresthesia	7%	31%
Dizziness	7%	0%
Insomnia	7%	0%
Oropharyngeal Pain	7%	0%

At 56 days, the percent change in body weight was +1.1±2.8% in the placebo group and -5.0±3.4% in the phentermine/topiramate group (placebo-subtracted weight loss of 6.1%). Owing to the relatively small sample size and the fact that weight reduction was a secondary outcome variable, the manufacturer did not perform a statistical analysis on these results. However, the preliminary results further support our estimated treatment effect, particularly considering the treatment period was only two months (56 days). Indeed, the degree of placebo-subtracted weight loss was slightly better than what was observed in the adult trials at the two-month time-point, suggesting that the effects are at least additive when these two medications are used together.

In summary, this portfolio of preliminary work: 1) demonstrates our Center's leadership role in, and commitment to, the field of pediatric obesity medicine; 2) highlights the benefits (short-term weight loss and cardiometabolic risk factor improvement) and limitations (long-term weight regain) of meal replacement therapy as well as our experience with this intervention; 3) provides preliminary evidence of the safety/efficacy of phentermine and topiramate monotherapy in the target population; 4) demonstrates the clinically-meaningful weight loss efficacy and safety profile of phentermine/topiramate combination therapy in adults; 5) provides preliminary evidence supporting the safety, efficacy, and acceptability of phentermine/topiramate combination therapy in adolescents with severe obesity; and 6) sets the stage for taking this next important step.

2.3 Primary Endpoint/Event/Outcome:

- *To evaluate the effects of phentermine/topiramate on weight loss maintenance and cardiometabolic risk factor improvements in adolescents (12 to <18 years old) with severe obesity*. We hypothesize that following initial BMI reduction with meal replacement therapy, 52 weeks of treatment with phentermine/topiramate vs. placebo will not only sustain, but further enhance reductions in BMI (primary endpoint), total body- and visceral-fat, cardiometabolic risk factors, inflammation, and oxidative stress.

2.4 Secondary Endpoint(s)/Event(s)/Outcome(s):

- *Perform a comprehensive panel of in-depth physiological assessments to characterize the safety of phentermine/topiramate*. Phentermine/topiramate will have an acceptable safety profile, demonstrating no statistically significant or clinically-meaningful differences from placebo in heart rate, blood pressure, cognition, mental health, or bone health.
- *Investigate mechanisms of action of phentermine/topiramate in counteracting biological forces favoring weight gain*. Compared to placebo, phentermine/topiramate will reduce appetite, enhance satiety, and increase resting and total energy expenditure.

3.0 Study Intervention(s)/Investigational Agent(s)

3.1 Description:

Lifestyle Modification/Behavioral Therapy and Counseling

All participants, regardless of drug/placebo assignment, will receive the same lifestyle/behavioral modification counseling monthly throughout the entire study: delivered at each in-person study visit and on the phone for months when there is no study visit. The lifestyle/behavioral modification curriculum has been adapted from the NIDDK-sponsored TODAY study lifestyle modification program materials[59] and is based on principles detailed in U.S. Preventive Services Task Force screening recommendation statement and utilized by our group in a previous[60] and ongoing trials. Trained study coordinators will deliver the lifestyle/behavioral modification counseling, which will focus on small, successive changes in dietary physical activity behaviors through the use of evidence-based behavior change strategies such as self-monitoring, goal setting, reinforcement for goal achievement, stimulus control, social support, problem solving, and motivational techniques. Selected sections of the educational materials will be reviewed and discussed at each face-to-face and phone-based lifestyle modification

counseling session. We have demonstrated the effectiveness of this lifestyle modification protocol in a randomized, placebo-controlled trial among adolescents with severe obesity.[60] To maximize generalizability and the interpretability of the findings, the frequency and intensity is intentionally designed to be practical, feasible and mimic the type and frequency of lifestyle counseling common to the clinic setting in pediatric weight management programs in the U.S.

Meal Replacement Induction Period

All participants will engage in a meal replacement induction period for six weeks with a goal of reducing individual BMI by at least 5%. Our group has experience successfully utilizing a similar meal replacement protocol in the target population as evidenced by over 70% of the adolescents with severe obesity in an unpublished study having achieved ≥5% BMI reduction in up to two months (as detailed in the preliminary data section). Berkowitz et al. have also demonstrated the utility of meal replacement therapy in adolescents with severe obesity.[50] Participants will be asked to strictly follow the eating regimen, which will include a total of approximately 1,200 kcals per day of commercially-available liquid shakes, pre-packaged frozen entrée meals, two servings of fruit, and three servings of vegetables. Shakes/meals will be provided free of charge – fruits/vegetables will be purchased by the participants. Guidance will be provided regarding the use of the meal replacement shakes or frozen entrees at school, and participants will be encouraged to engage in family meal sessions despite eating different foods. Participants who attend a school that does not have a microwave available for student use will be offered a letter to provide to the school so that they can make use of a microwave.

Medication and Placebo Administration, Dosing, and Compliance

Participants will be randomized (1:1) to phentermine/topiramate or placebo immediately following the meal replacement induction period (if successful in achieving ≥5% BMI reduction within the allotted six weeks). Participants randomized to phentermine/topiramate will initiate treatment at 3.75 mg/23 mg orally once daily in the morning for 14 days, which will then be increased to 7.5 mg/46 mg orally once daily in the morning for 14 days, which will then be increased to 11.25 mg/69 mg orally once daily in the morning for 14 days, which will then be increased to 15 mg/92 mg orally once daily in the morning for the remainder of the trial. Participants unable to tolerate the dosing regimen will be maintained at the maximally tolerated dose. All participants will undergo the same dose escalation process (although actual doses will vary by assignment) to maintain the blind nature of the design. Following the final study visit, all participants (including those

assigned to placebo) will be down-titrated gradually by taking medication every other day for seven days before stopping treatment altogether. Vivus Pharmaceuticals will donate phentermine/topiramate and placebo. Trial product will be managed by the University of Minnesota Investigational Drug Service Pharmacy. Participants will be instructed to take the medication under the supervision of a parent/guardian and pill counts of returned product will serve as a proxy of treatment compliance.

Study drug supply chain issues were identified in December of 2021. The impact of this at our site is that we do not have enough of the full dose of Qsymia (15 mg/92 mg) at this time and we have limited supply of the ¾ dose (11.25 mg/69 mg). The manufacturer believes that supply chain issues will be resolved in March-June of 2022 and they are working to be able to provide us with smaller shipments over the next 3-6 months. We have temporarily slowed recruiting for the project as a result of this issue. We have a commitment of the manufacturer to provide us with sufficient study drug/placebo supply if we enroll at a rate of approximately 3-4 participants per month. Participants who are currently at ½ dose will continue to titrate up according to the protocol, but when they get to the full dose, we will ask them to take two pills per day of the ½ dose tablets (to achieve full dose). We believe we have adequate supply of the ½ dose at our site to accommodate participants until supply of the full dose becomes available.

Should the study drug supply chain issues not be resolved in 3-6 months and we are depleting our supply of the study drug, we would ask that participants taper off the study medication. This will be accomplished by asking participants to take a dose every other day for one week before stopping the study medication. We have ample supply for a down-titration, should study drug supply chain issues persist.

3.2 Drug/Device Handling:

The phentermine/topiramate that will be used for this study will be stored with Investigational Drug Services (IDS). The IDS office specializes in storing and dispensing investigational drugs for clinical trials. Study physicians will write a prescription in order for IDS to dispense the medication. IDS is in a secure facility (behind two locked doors) and maintains refrigerators and freezers with temperature tracking to assure that the drugs utilized in this study will maintain stability. IDS will keep detailed records on the receipt of investigational product (including lot numbers) and detailed records on the dispensing of product to each subject enrolled in the study. IDS is also

equipped to destroy any medication that is returned at the end of the study when all drug accountability has been completed.

3.3 Biosafety:
Not applicable

3.4 Stem Cells:
Not applicable

4.0 Procedures Involved

4.1 Study Design:

This will be a randomized, double-blind, placebo-controlled clinical trial specifically designed to evaluate the ability of phentermine/topiramate to improve weight loss maintenance following a short-term (six weeks) meal replacement induction period among approximately 100 adolescents with severe obesity. Because the trial is designed to evaluate weight loss maintenance, participants must achieve at least 5% BMI reduction at week six of the meal replacement period in order to be randomized. Participants who do not achieve 5% BMI reduction will not continue in the trial. After achieving the 5% BMI reduction goal, participants will be randomized (1:1) to phentermine/topiramate or placebo for an additional 52 weeks while engaging in lifestyle modification therapy.

The goal of 5% BMI reduction over a period of six weeks is realistically-achievable based on our experience using a similar protocol in the target population, in which over 70% were able to lose the required amount of weight, and based on data reported by Berkowitz et al.,[50] which utilized meal replacement therapy. Estimating that 70% will meet the 5% BMI reduction benchmark during the induction period and considering a dropout rate of up to 20% *after* randomization (conservative estimate from our experience; note that one of the advantages of the meal replacement run-in period is that it will "weed out" individuals most likely to withdraw early in the trial, prior to randomization), we will enroll approximately 100 participants with the expectation that we will randomize approximately 60 participants.

The schedule of events section (below) shows the data that will be collected at each study visit. Following randomization, phone calls will be made monthly to assess adverse events and compliance and deliver lifestyle modification therapy. All participants will receive reimbursement for completing study visit assessments.

Schedule of Events

	Screening	**Baseline**	**Randomization** (six weeks from baseline)	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 30**	**Week 34**	**Week 39**	**Week 43**	**Week 47**	**Week 52**
Allowable window[#]			±3 d	± 3 d	± 7d	± 7d	± 7d	± 7d	± 7d	± 7d	± 7d	± 7d	± 7d	± 7d	± 7d
Consent	X														
Demographics and Environmental assessment[1]	X														
Review inclusion/exclusion		X													
Physical exam	X														X
Tanner staging	X														X
Comprehensive Metabolic Panel	X	X[2]	X	X		X			X			X			X
Pregnancy test	X	X	X	X		X			X			X			X
Hemoglobin A1c	X		X						X						X
Thyroid Stimulating Hormone (TSH)			X												X
Follicle Stimulating Hormone (FSH)			X												X
Luteinizing Hormone (LH)			X												X
Testosterone			X												X
Estradiol			X												X
Dehydroepiandrosterone (DHEAS)			X												X
Lipid Panel (total cholesterol, DHL, LDL and triglycerides)		X	X						X						X
Glucose		X	X						X						X
Insulin		X	X						X						X
C-Reactive Protein		X	X						X						X
Oxidized LDL		X	X						X						X
At home monthly urine pregnancy test[9]					X		X	X		X	X		X	X	
BMI/anthropometrics[4]	X	X	X	X	X	X			X			X			X
iDXA [5]		X	X						X						X
ECG	X														
Neuropsychological Function Testing[6]		X	X						X						X
Physical Activity and Eating Behavior Questionnaires[7]		X	X						X						X
Bone age		X													X
Resting metabolic rate		X	X						X						X
Total energy expenditure (N=60)		X	X						X						X

400-meter walk test		X	X						X						X
Blood pressure and heart rate	X	X	X	X	X	X			X			X			X
Depression and Suicide Screening[8]	X	X	X	X	X	X			X			X			X
AE assessment[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance assessment[10]			X	X	X	X	X	X	X	X	X	X	X	X	X
Lifestyle counseling[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraceptive counseling[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review of concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensing			X	X	X	X			X			X			X

Allowable window is ± 3d for the Randomization visit (from baseline), ± 3d for the Week 4 visit and± 7d from the Randomization visit for the visits at Weeks 8,12, 16, 20, 26, 30, 34, 39, 43, 47, and 52.

1 Demographics to include age, sex, race, ethnicity, home address, total combined family income, parents' level of education, parents' employment status. Environmental assessment to include Food Security Screen, Social Support for Eating Habits, Social Support for Exercise, ACE-Q Teen (Adverse Childhood Event)

2 Comprehensive metabolic panel does not need to be repeated at Baseline if it occurs within 30 days of screening..

4 Height, weight, waist measurement, BMI, hip circumference. Heart rate will be collected at Screening.

5 iDXA to include total/regional body fat and BMC

6 Neuropsychological Functioning to include NIH Toolbox (cognition battery), PROMIS-Anxiety, Impact of Weight on Quality of Life-Kids (IWQOL-Kids)

7 Physical Activity and Eating Behavior Questionnaires to include Visual Analog Scale of Self-Reported Appetite and Satiety, Questionnaire of Eating and Weight Patterns, Adult Eating Behavior Questionnaire (AEBQ), Reward Based Eating Drive Scale X5 (RED-5, hedonic eating), Dutch Eating Behavior Questionnaire (DEBQ) and the Physical Activity Questionnaire for Adolescents (PAQ-A)

8 Depression and Suicide Screening to include the PHQ-9 and the Columbia-Suicide Severity Rating Scale (C-SSRS)

9 Females of childbearing potential will be asked to conduct at home urine pregnancy tests every month where there is not an in-person visit. Urine pregnancy tests will be provided to the participant.

10. Adverse events and compliance assessments will be done over the phone at Weeks 16, 20, 30, 34, 43 and 47.

11. Lifestyle counseling will be done over the phone at Weeks 16, 20, 30, 34, 43 and 47

12. Contraceptive counseling including the two methods of contraception being utilized will be completed at all visits, including telephone visits.

4.2 Study Procedures:

Anthropometric Measurements and Quantification of Total Body- and Regional-Fat Depots

Height and weight will be measured using a calibrated, wall-mounted stadiometer and an electronic scale, respectively. Measurements will be obtained with participants in light clothing, without shoes. Two consecutive height and weight measurements will be obtained and averaged. If the first two values differ by more than 0.5 cm for height and/or 0.3 kg for weight, a third measurement will be obtained and the average of three measurements will be calculated. BMI will be calculated as the weight in kilograms divided by the height in meters, squared. Waist circumference will be measured at end-expiration midway between the base of the rib cage and the superior iliac crest. Hip circumference will be measured at the maximal protuberance of the buttocks. Total percent body fat, visceral fat, and lean mass will be determined by dual energy x-ray absorptiometry (iDXA, GE Healthcare). The scanning table accommodates body sizes of up to 204 kg. Our group has done some of the early work regarding validation of iDXA visceral fat in children and adolescents.[6]

Pubertal Development, Blood Pressure, and Blood Analyses

All Tanner staging will be conducted by individuals trained in assessing Tanner stage. Blood pressure measurements will be obtained manually on the same arm using the same cuff size and equipment. Standardized procedures will be employed as described previously.[61] Individual cuff size will be determined by measuring the arm circumference midway between the acromial process and the bony olecranon. Sitting blood pressure and heart rate will be measured after the participant has been resting quietly for 10 minutes. Measurements will be made three consecutive times (3-minute intervals). The final two of three measurements will be averaged. Fasting (≥12 hours) blood will be collected for the measurement of lipids (total-, LDL-, HDL-cholesterol, and triglycerides), glucose, insulin, hemoglobin A1c, and pubertal hormones (assayed in Fairview Diagnostics Laboratories, Minneapolis, MN - a Center for Disease Control and Prevention certified laboratory). Additional blood for C-reactive protein and oxidized LDL cholesterol will be processed and stored at -80 degrees C for a batched analysis in the University of Minnesota Cytokine Reference Laboratory (CLIA licensed).

Measurement of Resting Metabolic Rate and Total Energy Expenditure

Resting metabolic rate will be measured by indirect calorimetry after participants have been fasting for ≥12 hours. Metabolic data will be

collected using a ventilated hood (Parvo Medics; Sandy UT). Previous investigations have shown the ventilated hood method to be more accurate and reliable when compared to the other techniques.[62, 63] This method has been shown to be more comfortable in tests that last more than 5-10 minutes.[63] Participants will be instructed to not engage in exercise on the day prior to testing. Resting gas exchange measurements will be collected using a Parvo Medics TrueOne 2400 Metabolic Cart, (Sandy, UT). The cart will be calibrated for gas analyses and volume at least twice prior to each test session. Room air (25°C) will be drawn through the hood at a rate of 40 L/min. Resting metabolic rates will be collected over the initial 30-minute reclining period with the last 10-minutes averaged into an estimate of resting metabolic rate.

Total daily energy expenditure will be measured in a subset of participants (N = 60) during a one-week period by the doubly-labeled water method, which employs the stable isotopes deuterium (^{2}H) and oxygen-18 (^{18}O). This method provides the most accurate assessment of free-living daily energy expenditure. It is based upon the principle that the doubly labeled water is rapidly distributed into body water. Oxygen atoms are eliminated from the body as both H_2O and exhaled CO_2, whereas hydrogen atoms are eliminated as H_2O only. Therefore, the rate of disappearance of deuterium reflects water turnover and the rate of disappearance of ^{18}O represents water turnover as well as CO_2 production. The difference between the elimination rates of oxygen and hydrogen from body water represent a measure of CO_2 flux, which is proportional to total energy expenditure. Each sample will be analyzed for $H_2{}^{18}O$ and $^{2}H_2O$ abundances by isotope ratio mass spectrometry.

400-Meter Walk Test

- Limitation in ability to walk is an important outcome of severe obesity. Walking ability and endurance can be directly assessed by performance testing. The 400-meter walk test has been shown to be related to VO2 max (the maximum volume of oxygen consumed by the body each minute during exercise, while breathing air at sea level); thus, the walk not only tests ability to walk but physical fitness. To eliminate the effect of different footwear on test performance, the test should be performed in tennis shoes or comfortable walking shoes with minimal or no heels. Participants will be instructed prior to the visit that they should wear or bring appropriate shoes to the clinic. Participants wearing footwear that impedes their walking should be excluded from the test. Participants with the following issues/conditions will not

participate in the 400-meter walk test: those who use a walking aid; participants whose systolic blood pressure (SBP) is > 180 mmHg or whose diastolic blood pressure (DBP is > 100 mmHg); whose ECG at screening shows atrial fibrillation or atrial flutter; Wolff-Parkinson-White or ventricular pre-excitation, idioventricular rhythm, ventricular tachycardia, third degree or complete A-V block, any evidence of acute injury or acute ischemia or marked T-wave abnormality.

Visual Analog Scales and Standardized Questionnaires

We will obtain self-report ratings (average over the preceding week) on 15-cm visual analog scales anchored with "not at all" to "extremely" for appetite and satiety. This method has been validated for use in appetite research[64] and was utilized by Sysko et al. in a study of adolescents with severe obesity.[65] Self-reported appetite and satiety will also be measured using the Adult Eating Behavior Questionnaire (AEBQ); note: in our experience, the self-report version (AEBQ) is more appropriate for adolescents vs. the child version (CEBQ). Binge eating behaviors/features will be measured with the Reward Based Eating Drive Scale X5 (RED-5) Additional relevant eating behavior domains are addressed in the AEBQ including emotional overeating and enjoyment of food (hedonic eating) and will be captured in supplemental questionnaires: Dutch Eating Behavior Questionnaire, and Questionnaire of Eating and Weight Patterns – Adolescent Questionnaires will allow us to examine the impact of eating behaviors in relation to weight loss response; results will be considered hypothesis-generating. Quality of life will be assessed via the IWQOL-kids (weight-related quality of life). Physical activity of participants will be measured with the PAQ-A.

Safety-Related Assessments

Comprehensive metabolic panels will be performed at regular intervals throughout the study and may be performed more often if a participant has values that warrant closer monitoring. Pregnancy test (for girls) will be performed at all in-person study visits. Urine pregnancy tests will be provided to females of childbearing potential to be taken at home with results reported to the study team monthly when there is not a scheduled in-person visit. We will require all female participants to confirm use of two forms of contraception if sexually active with males. Effective contraception is defined as double barrier methods, stable hormonal contraception plus single barrier method, tubal ligation, or abstinence. We will instruct all females who miss a menstrual period or when pregnancy is otherwise suspected to perform a pregnancy test. We will monitor for potential changes in heart rate and arrhythmias (ECG), depression, suicidal behavior

and ideation, acute myopia and secondary angle closure glaucoma, mood and sleep disorders, cognitive impairment, metabolic acidosis, and elevated creatinine. Sexual maturation (Tanner stage) and stature will be measured at baseline and 52 weeks for those less than Tanner 5 at baseline. A panel of related biomarkers (TSH, FSH, LH, testosterone, estradiol, and DHEAS) will be measured at randomization and 52 weeks. Changes in neurocognitive function will be evaluated with questionnaires and computer-based assessments including the NIH Toolbox. Bone mineral content will be measured by iDXA. Bone age will be measured at baseline and 52 weeks for those who have not reached complete bone maturation at baseline.

Subjects will be assessed for depression and suicide with the Patient Health Questionnaire-9 [PHQ-9] and the Columbia-Suicide Severity Rating Scale [C-SSRS] at each in person visit and the results will be reviewed by a staff member while the participant is still present at the visit. Participants (and their parents, if the participant is a minor) will be referred to a mental health professional (MHP) or to their primary care provider if the subject has a PHQ-9 score of >15, any suicidal behavior, or any suicidal ideation of type 4 or 5 on the C-SSRS. They will also be provided with the contact information for the nationwide Suicide and Crisis Lifeline (telephone 988 or 988lifeline.org). If the participant endorses current (in that moment), active suicidal ideation with plan and intent, they will also be referred to the emergency department. Participants (and their parent) will be asked if they feel safe enough to leave the research clinic and with the established plan. The decision as to whether the participant will be allowed to continue in the trial will be made by the local medical monitor in consultation with the MHP or primary care provider after the referral clinical visit.

4.3 Study Duration:

Fifty-eight weeks (six weeks of meal replacement therapy followed by 52 weeks of medication/placebo treatment)

4.4 Individually Identifiable Health Information:
Please see PHI Section 16.0

4.5 Use of radiation*:*

This study will consist of up to two bone age (wrist) x-rays and iDXA scans, both of which utilize ionizing radiation. None of the tests done for this study are considered part of standard medical care. There will be up to two bone age (wrist) x-rays for the study. Each x-ray consists of exposure to 0.001 mSv. There will be a total of 4 iDXA scans for the study. Each iDXA consists of exposure to 0.01 mSv. The anticipated total amount of radiation that an

individual would receive from participating in this study is estimated to be 0.044 mSv. In comparison, a resident of the State of Minnesota receives approximately 3 mSv from natural background radiation as a result of living in Minnesota.

4.6 Use of Center for Magnetic Resonance Research*:*
Not applicable

5.0 Data and Specimen Banking

5.1 Storage and Access:
Blood samples for lipids (total-, HDL-, and LDL-cholesterol and triglycerides), glucose, insulin, hemoglobin A1c and pubertal hormones will be sent to the Fairview Diagnostics Laboratory (which is CLIA licensed) after collection of the sample. Blood samples for C-reactive protein and oxidized LDL cholesterol will be stored in a -80 C freezer and analyzed en masse for analysis at the University of Minnesota Cytokine Reference Laboratory, which is CLIA licensed.

5.2 Data:
Results from the Fairview Diagnostics Laboratories will be posted to chart and will also be logged into REDCap. The results for the samples analyzed by the University of Minnesota Cytokine Reference Laboratory will be logged into REDCap.

5.3 Release/Sharing:
Access to the study's data in REDCap will be restricted to the members of the study team by username and password.

6.0 Sharing of Results with Participants

6.1 Sharing Results:
Results from laboratory tests analyzed by the Fairview lab will be posted to the participant's medical record. Results of the testing conducted by the University of Minnesota Cytokine Reference Laboratory will not be shared and will be analyzed en masse at the end of the study.

6.2 Sharing Genetic Results:
Not applicable

7.0 Study Population

7.1 Inclusion Criteria:

- Severe obesity (BMI >/= 120% of the 95th percentile or BMI >/= 35 kg/m^2

- Age 12 to < 18 years of age at enrollment (screening) and Tanner stage >/=2
- Female participants who are sexually active with males and who are able to get pregnant must agree to use two forms of contraception throughout the trial

Exclusion Criteria:

- Diabetes (type 1 or 2)
- Current or recent (< six months prior to enrollment) use of anti-obesity medication(s) defined as orlistat, phentermine, topiramate, combination phentermine/topiramate, liraglutide, and/or combination naltrexone/bupropion (monotherapy use of naltrexone or bupropion is not an exclusion)
- Previous metabolic/bariatric surgery
- Current use of a stimulant medication
- History of glaucoma
- Current or recent (<14 days) use of monoamine oxidase inhibitor
- Known hypersensitivity to sympathomimetic amines
- Any history of treatment with growth hormone
- Any history of bulimia nervosa
- Major psychiatric disorder as determined by the local medical monitor
- Unstable and clinically-diagnosed (defined as documented in the medical record, if available) depression
- Any history of active suicide attempt
- History of suicidal ideation or self-harm within the previous 30 days of screening
- PHQ-9 score >15 at screening
- Current pregnancy or plans to become pregnant during study participation
- Current tobacco use
- ALT or AST >/= 3 times the upper limit of normal
- Bicarbonate <18 mmol/L
- Creatinine > 1.2 mg/dL
- Any history of seizures (with the exception of febrile seizures)
- Uncontrolled hypertension as determined by the local medical monitor
- History of structural heart defect or clinically significant arrhythmia
- Diagnosed monogenic obesity
- Any history of cholelithiasis
- Any history of nephrolithiasis

- Clinically diagnosed hyperthyroidism
- Untreated thyroid disorder
- Any disorder, unwillingness, or inability, not covered by any other exclusion criteria, which in the investigator's opinion, might jeopardize the subject's safety or compliance with the protocol

7.2 *Screening Visit*

At this visit, the subject's parent/legal guardian will be taken through and the consent process and sign the parental consent form and the subject will be asked to sign the assent form after they have had the opportunity to learn about the study and ask any questions that they may have. The subject will undergo the following:

- BMI and Anthropometrics: height, weight, waist measurement, BMI, hip circumference.
- Blood pressure and heart rate.
- Physical examination and Tanner staging by a physician.
- Blood draw for comprehensive metabolic panel, hemoglobin A1c. Pregnancy test for females
- Electrocardiogram.
- Demographics/Environmental assessment.
- Depression and Suicide Screening with PHQ-9 and C-SSRS
- Contraceptive counseling
- Review of medications

Baseline Visit (within 30 days of screening)

Subjects will be asked to present at this visit after having fasted for at least 12 hours. Their medical and medication history will be reviewed against the study inclusion/exclusion criteria. The subject will undergo the following:

- Blood draw for comprehensive metabolic panel (if this visit is more than 30 days after the Screening visit), fasting lipid panel, glucose and insulin. A pregnancy test for females
- Blood will be drawn and banked for biomarker testing (C-reactive protein and oxidized LDL) which will be analyzed in masse at the conclusion of the study.
- BMI and Anthropometrics: height, weight, waist measurement, BMI, hip circumference
- iDXA to include total/regional body fat and BMC.
- Neurocognitive testing (NIH Toolbox, PROMIS-Anxiety, Impact of Weight on Quality of Life-Kids (IWQOL-Kids))
- Bone age x-ray
- Resting metabolic rate

- Total energy expenditure in subset (N=60) including drop-off of urine samples
- 400-meter walk test
- Blood pressure and heart rate
- Questionnaires (Visual Analog Scale of Patient Reported Appetite and Satiety, Questionnaire of Eating and Weight Patterns-Adolescent (QEWP-A), Adult Eating Behavior Questionnaire (AEBQ), Reward Based Eating Drive Scale (RED-5, hedonic eating scale), Dutch Eating Behavior Questionnaire (DEBQ) and Physical Activity Questionnaire for Adolescents (PAQ-A)
- Depression and Suicide Screening with PHQ-9 and C-SSRS
- Lifestyle counseling
- Contraceptive counseling
- Review of concomitant medications
- Review of adverse events

Randomization (six weeks±3 days from baseline)
After six weeks of meal replacement therapy, subjects achieving the BMI reduction goal will be randomized (1:1 ratio) to either phentermine+topiramate or to placebo. The following items will happen at the visit:

- Blood draw for comprehensive metabolic panel, hemoglobin A1c, TSH, FSH, LH, testosterone, estradiol, DHEAS, lipid panel, glucose and insulin. A pregnancy test for females.
- Blood will be drawn and banked for biomarker testing (C-reactive protein and oxidized LDL) which will be analyzed en masse at the conclusion of the study.
- BMI and Anthropometrics: height, weight, waist measurement, BMI, hip circumference
- iDXA to include total/regional body fat and BMC.
- Neurocognitive testing (NIH Toolbox, PROMIS-Anxiety, Impact of Weight on Quality of Life-Kids (IWQOL-Kids))
- Resting metabolic rate
- Total energy expenditure in a subset (N=60), including drop-off of urine samples
- 400-meter walk test
- Blood pressure
- Questionnaires (Visual Analog Scale of Patient Reported Appetite and Satiety, Questionnaire of Eating and Weight Patterns-Adolescent (QEWP-A), Adult Eating Behavior Questionnaire (AEBQ), Reward Based Eating Drive Scale (RED-5, hedonic eating scale), Dutch Eating Behavior Questionnaire (DEBQ)

- AE assessment
- Compliance assessment
- Depression and Suicide Screening with PHQ-9 and C-SSRS
- Lifestyle counseling
- Contraceptive counseling
- Review of concomitant medications
- Study drug dispensing with instructions on the up-titration schedule

Week 4 (±3 days from Randomization)

- Blood draw for a comprehensive metabolic panel. A pregnancy test for females.
- BMI and Anthropometrics: height, weight, waist measurement, BMI, hip circumference
- Blood pressure
- AE assessment
- Compliance assessment
- Depression and Suicide Screening with PHQ-9 and C-SSRS
- Lifestyle counseling
- Contraceptive counseling
- Review of concomitant medications
- Study drug dispensing with instructions on the up-titration schedule

Week 8 (± 7days from Randomization)

- BMI and Anthropometrics: height, weight, waist measurement, BMI, hip circumference
- Blood pressure
- AE Assessment
- Compliance Assessment
- Depression and Suicide Screening with PHQ-9 and C-SSRS
- Lifestyle Counseling
- Contraceptive counseling
- Review of concomitant medications
- At home pregnancy test (for females of childbearing potential)
- Study drug dispensing with instructions on the up-titration schedule

Week 12 (± 7days from Randomization)

- Blood draw for a comprehensive metabolic panel. A pregnancy test for females.
- BMI and Anthropometrics: height, weight, waist measurement, BMI, hip circumference
- Blood pressure

- AE assessment
- Compliance assessment
- Depression and Suicide Screening with PHQ-9 and C-SSRS
- Lifestyle counseling
- Contraceptive counseling
- Review of concomitant medications
- Study drug dispensing with instructions on the up-titration schedule

Telephone Visit Week 16 (± 7days from Randomization)

- AE Assessment
- Compliance Assessment
- Lifestyle Counseling
- Contraceptive counseling
- Review of concomitant medications
- At home pregnancy test (for females of childbearing potential)

Telephone Visit Week 20 (± 7days from Randomization)

- AE Assessment
- Compliance Assessment
- Lifestyle Counseling
- Contraceptive counseling
- Review of concomitant medications
- At home pregnancy test (for females of childbearing potential)

Week 26 (± 7days from Randomization)

- Blood draw for a comprehensive metabolic panel, hemoglobin A1c, lipid panel, glucose, and insulin. A pregnancy test for females.
- Blood will be drawn and banked for biomarker testing (C-reactive protein and oxidized LDL) which will be analyzed en masse at the conclusion of the study.
- BMI and Anthropometrics: height, weight, waist measurement, BMI, hip circumference
- iDXA to include total/regional body fat and BMC.
- Neurocognitive testing (NIH Toolbox, PROMIS-Anxiety, Impact of Weight on Quality of Life-Kids (IWQOL-Kids))
- Resting metabolic rate
- Total energy expenditure in a subset (N=60), including drop-off of urine samples
- Blood pressure
- 400-meter walk test

- Questionnaires (Visual Analog Scale of Patient Reported Appetite and Satiety, Questionnaire of Eating and Weight Patterns-Adolescent (QEWP-A), Adult Eating Behavior Questionnaire (AEBQ), Reward Based Eating Drive Scale (RED-5, hedonic eating scale), Dutch Eating Behavior Questionnaire (DEBQ), and PAQ-A
- AE assessment
- Compliance assessment
- Depression and Suicide Screening with PHQ-9 and C-SSRS
- Lifestyle counseling
- Contraceptive counseling
- Review of concomitant medications
- Study drug dispensing with instructions on the up-titration schedule

Telephone Visit Week 30 (± 7days from Randomization)

- AE Assessment
- Compliance Assessment
- Lifestyle Counseling
- Contraceptive counseling
- Review of concomitant medications
- At home pregnancy test (for females of childbearing potential)

Telephone Visit Week 34 (± 7days from Randomization)

- AE Assessment
- Compliance Assessment
- Lifestyle Counseling
- Contraceptive counseling
- Review of concomitant medications
- At home pregnancy test (for females of childbearing potential)

Week 39 (± 7days from Randomization)

- Blood draw for a comprehensive metabolic panel. A pregnancy test for females.
- BMI and Anthropometrics: height, weight, waist measurement, BMI, hip circumference
- Blood pressure
- AE assessment
- Compliance assessment
- Depression and Suicide Screening with PHQ-9 and C-SSRS
- Lifestyle counseling
- Contraceptive counseling
- Review of concomitant medications

- Study drug dispensing with instructions on the up-titration schedule

Telephone Visit Week 43 (± 7days from Randomization)

- AE Assessment
- Compliance Assessment
- Lifestyle Counseling
- Contraceptive counseling
- Review of concomitant medications
- At home pregnancy test (for females of childbearing potential)

Telephone Visit Week 47 (± 7days from Randomization)

- AE Assessment
- Compliance Assessment
- Lifestyle Counseling
- Contraceptive counseling
- Review of concomitant medications
- At home pregnancy test (for females of childbearing potential)

Week 52 (± 7days from Randomization)

- Physical examination and Tanner staging (if necessary)
- Blood draw for comprehensive metabolic panel, hemoglobin A1c, TSH, FSH, LH, testosterone, estradiol, DHEAS, lipid panel, glucose, and insulin. A pregnancy test for females.
- Blood will be drawn and banked for biomarker testing (C-reactive protein and oxidized LDL) which will be analyzed en masse at the conclusion of the study.
- BMI and Anthropometrics: height, weight, waist measurement, BMI, hip circumference
- iDXA to include total/regional body fat and BMC.
- Neurocognitive testing (NIH Toolbox, PROMIS-Anxiety, Impact of Weight on Quality of Life-Kids (IWQOL-Kids))
- Bone age x-ray, if necessary
- Resting metabolic rate
- Total energy expenditure in a subset (N=60), including drop-off of urine samples
- Blood pressure
- 400-meter walk test
- Questionnaires (Visual Analog Scale of Patient Reported Appetite and Satiety, Questionnaire of Eating and Weight Patterns-Adolescent (QEWP-A), Adult Eating Behavior Questionnaire (AEBQ), Reward

Based Eating Drive Scale (RED-5, hedonic eating scale), Dutch Eating Behavior Questionnaire (DEBQ) and PAQ-A

- AE assessment
- Compliance assessment
- Depression and Suicide Screening with PHQ-9 and C-SSRS
- Lifestyle counseling
- Review of concomitant medications
- Instructions on dose down-titration and stopping the study medication

8.0 Vulnerable Populations

8.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study.
Children	Targeted Population
Pregnant women/fetuses/neonates	Excluded from Participation
Prisoners	Excluded from Participation
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded from Participation
Non-English speakers	Excluded from Participation
Those unable to read (illiterate)	Excluded from Participation
Employees of the researcher	Excluded from Participation
Students of the researcher	Excluded from Participation
Undervalued or disenfranchised social group	Included/Allowed to Participate

Active members of the military (service members), DoD personnel (including civilian employees)	Excluded from Participation
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded from Participation
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Included/Allowed to Participate
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Included/Allowed to Participate
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Included/Allowed to Participate
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded from Participation

8.2 Additional Safeguards:
Not applicable

9.0 Local Number of Participants

9.1 Local Number of Participants to be Consented:

More than 120 – we anticipate needing to consent/assent approximately 200 owing to potential screen failures.

10.0 Local Recruitment Methods

10.1 Recruitment Process

Our recruitment process will be four-fold: we will leverage the MN-POC for recruitment. Member institutions include the University of Minnesota, Mayo Clinic, Children's Hospitals and Clinics of Minnesota, and Park Nicollet/HealthPartners, which represent a large portion of the pediatric medical care provided in Minnesota. We plan on reaching out to physicians in these member institutions and letting them know about the study so that they could refer patients who come into their clinics. We may also work with these and other local health systems to have them send recruitment letters on our behalf to potentially eligible participants. The second method will be to have BPIC run queries and get an eligible patient list and mail out letters, making certain to not put on the mailing list the patients who have opted out of being contacted about potential research projects. We will also ask BPIC to run queries of patients who are waiting for appointments to be seen in the Pediatric Weight Management Clinic for the first time and who are on the waitlist to have an appointment scheduled in the Pediatric Weight Management Clinic. Interested participants will be asked to contact the study team and up to three follow-up phone calls will be made by study staff if no initial response is received. The follow-up phone call limit does not apply to situations of "phone-tag." Identification of Potential Participants:
Both the referrals from MN-POC and the recruitment mailings will request that interested parties contact the research staff for additional information. If the interested party and the research staff do not connect on the first try, the research staff will attempt to contact the interested parties with up to three follow-up phone calls. The follow-up phone call limit does not apply to situations of "phone-tag." The fourth method will be to partner with the Minneapolis YWCA to add information to their 'Mission in Action e-newsletter. The newsletter reaches people involved with the YWCA Minneapolis through program participants, fitness members, donors, event attendees, and supporters.

10.2 Recruitment Materials:

A recruitment letter and recruitment flyers will be created for this study and approved by the IRB before use. A small paragraph to be included in the 'Mission in Action e-newsletter' will be created for this study and approved by the IRB before use.

10.3 Payment:

We would like to recognize that participation in this study is time intensive for the subject and their family members. Participants will earn up to $960 for their time and effort. Payment will be made via the Greenphire ClinCard on the following schedule:

- Screening visit: $100

- Baseline visit: $100
- Randomization visit: $100 (including participants who do not make the BMI goal)
- Week 4 visit: $100
- Week 8 visit: $100
- Week 12 visit: $100
- Week 26 visit: $100
- Week 39 visit $100
- Week 52 visit: $100
- Phone visits: $10 per visit, if all 6 visits are completed, a total of $60 will be provided

Participants will also receive incentive payment for the number of lifestyle visits conducted by telephone that they complete. This payment will be made after the Week 52 visit or earlier if the participant leaves the study early. This brings the total an individual can earn up to $1060. The payment will be applied to the ClinCard.

- 3 or more therapy visits: $25 bonus
- 6 or more therapy visits plus the Week 52 visit: $75 bonus

Participants who are selected to be part of the calorie expenditure testing using doubly labeled water will receive additional payments for the time and effort that it takes to collect urine and drop it off 7 days after the following visits. Participants selected for the calorie expenditure testing can receive an additional $80, bringing the maximum they can earn up to $1140:

- Baseline + 7 days: $20
- Randomization + 7 days: $20
- Week 26 + 7 days: $20
- Week 52 + 7 days: $20

Parents/guardians attending the baseline, randomization, 26-week, and 52-week visits will be offered a meal voucher or Greenphire ClinCard for a meal ($10 value) since these visits are long in duration.

11.0 Withdrawal of Participants

11.1 Withdrawal Circumstances:

Subjects will be allowed to withdraw from the study at any time. Subjects will be asked to taper the study medication as outlined by the medical safety officer in order to be safely removed from the study medication. This is typically done by taking one dose every other day for at least one week prior

to stopping, but this may be tailored for each individual based on the medical safety officer's assessment. After the taper is complete, will be asked to return for one final visit and to return any study medication. Subjects may be withdrawn from the study at any time based upon investigator judgement and subjects may be asked to taper the study medication if they are removed from the study in order to ensure subject safety. Subjects who are not compliant with taking the study medication may be removed from the study.

In the event that a participant has a serious adverse event that is deemed related to the study medication and/or procedures by the lead investigator for medical safety (medical safety officer), the participant will be required to immediately discontinue the intervention.

11.2 Withdrawal Procedures:

Any subject who is removed from the study will be asked to return for one final visit to assess adverse events and to collect any unused study medication and do a final study medication compliance.

11.3 Termination Procedures:

It will be noted in the subject enrollment log that the subject has been discontinued from the study and the date of the last study related visit. No additional data will be collected after that time. Data that has already been collected can be used in the study analysis.

12.0 Risks to Participants

12.1 Foreseeable Risks:

Risks of blood sampling

There is minimal risk of bruising, fainting and infection associated with blood draws and IV placement.

Meal Replacement Therapy

All participants will engage in a meal replacement induction period with a goal of reducing individual BMI by at least 5%. Our group has experience successfully utilizing a similar meal replacement protocol in the target population. Meal replacements are commonly used in the clinical setting and this treatment approach is generally considered to be low-risk.

DXA, Bone Age, and Doubly-Labeled Water

The iDXA and bone age scans involve exposure to a very low dose of ionizing radiation. The average amount of radiation that the average person would receive from the iDXA and bone age scan is less than 1% (3 mrem) of that received from natural sources of radiation by a Minnesota resident in one year (300 mrem). The doubly labeled water test measures total energy expenditure over a 7-day period through the collection of urine samples. Participants will be asked to drink a glass of water that is enriched with two atoms which are called stable isotopes (non-radioactive) and provide periodic urine samples. The extra neutron in the doubly labeled water is not radioactive and therefore poses no risk. Previous studies have widely utilized this technique in both children and pregnant women.

Expected Adverse Events – Qsymia

Adverse events will be reviewed and documented at each study visit and phone call (monitored monthly throughout the study). Participants will be instructed to contact study staff immediately if any adverse event is experienced. Overall, the safety profile of Qsymia has been demonstrated to be acceptable in adults, with paresthesia (mild tingling in the extremities), dysgeusia (altered taste), insomnia, constipation, and dry mouth as the most commonly reported (incidence ≥5%). On rare occasions (less than 2%) Qsymia may cause a severe rash with blisters and peeling skin, especially around the mouth, nose, eyes and genitals. Qsymia should be discontinued at the first sign of a rash unless the rash is clearly not drug related. Of note, topiramate use during the first trimester of pregnancy is associated with an increased risk of oral clefts in the fetus. Comprehensive metabolic panels will be performed at routine intervals and more frequently while participants are starting the study medication. Pregnancy tests (for girls) will be performed at all in-person study visits. Female participants who are capable of getting pregnant will be provided with urine pregnancy tests to take at home on a monthly basis when there is no visit and they will be asked to report the results to the study team. We will require all female participants who are sexually active with males to confirm use of at least two forms of effective contraception. Effective contraception is defined as double barrier methods, stable hormonal contraception plus single barrier method, tubal ligation, or abstinence. We will instruct all females who miss

a menstrual period or when pregnancy is otherwise suspected to perform a pregnancy test. In addition, we will monitor for potential changes in depression, anxiety, suicidal behavior and ideation, acute myopia and secondary angle closure glaucoma, mood and sleep disorders, cognitive impairment, metabolic acidosis, and elevated creatinine. Sexual maturation (Tanner stage), stature, and a panel of related biomarkers will be measured including TSH, FSH, LH, testosterone, estradiol, and DHEAS. Individuals who abruptly stop taking phentermine/topiramate may be at risk of seizures. For this reason, it is recommended that individuals do not stop taking phentermine/topiramate abruptly and take a dose every other day for one week to help avoid this issue.

Changes in neurocognitive function will be evaluated with questionnaires and computer-based assessments including the NIH Toolbox, PROMIS-Anxiety anxiety and IWQOL-Kids. Bone mineral content will be measured by iDXA. Bone age will be measured during the trial. Our group has experience utilizing these tests within the context of previous clinical trials in adolescents with severe obesity.

12.2 Reproduction Risks:

All female participants who are sexually active with males must agree to use two forms of birth control during their time in the study. Effective contraception is defined as double barrier methods, stable hormonal contraception plus single barrier method, tubal ligation, or abstinence. We will instruct all females who miss a menstrual period or when pregnancy is otherwise suspected to perform a pregnancy test. Females of childbearing potential will have urine pregnancy at each in-person visit and will be asked to perform urine pregnancy tests at home monthly (kit provided).

12.3 Risks to Others:

Not applicable

12.4 Definition of Adverse Events:

An adverse event is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event can be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associate with the use of a medical product.

12.5 Definition of Adverse Events:

An SAE is an AE that fulfills at least one of the following criteria:

- Results in death

- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent disability/incapacity
- Is a congenital anomaly/birth defect

12.6 Classification of an Adverse Event:

Severity of Event. The severity of all AEs will be assessed by the study clinician using the following grading system

- Grade 1: Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily life
- Grade 4: Life-threatening: urgent intervention indicated
- Grade 5: Death related to adverse event

Relationship to Study Intervention: All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Not Related: clearly not related to the investigational agent(s)
- Unlikely: doubtfully related to the investigational agent(s)
- Possible: may be related to the investigational agent(s)
- Probable: likely related to the investigational agent(s)
- Definite: clearly related to the investigational agent(s)

Expectedness: The study clinician will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

12.7 Time Period and Frequency for Event Assessment and Follow-Up:

All AEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time

of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

The study staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days (for non-serious AEs) and 30 days (for SAEs) after the last day of study participation. At each study visit, the study staff will inquire about the occurrence of AEs/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The PI will notify the IRB of any SAE that meets the definition of being an unanticipated problem that involves risk to subjects or others (UPIRTSO) within five days of knowledge of the event. The PI will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected SAE as soon as possible, but in no case later than 7 calendar days after the PI's initial receipt of the information. Non-fatal or non-life-threatening SAEs will be reported to the FDA no later than 15 calendar days after the PI's initial receipt of the information.

The DSMB will be provided with AE and SAE information prior to their review of the study, at least every six months.

13.0 Potential Benefits to Participants

13.1 Potential Benefits:

We believe the potential benefits to the participants outweigh the risks in this study. We expect that most, if not all, participants will experience some degree of weight loss and cardiometabolic risk factor improvements during the meal replacement period. Furthermore, participants randomized to receive phentermine+topiramate may benefit further. Since data from clinical trials in adults have demonstrated reduction in BMI and improvements in cardiometabolic risk factors with phentermine+topiramate treatment, it is reasonable to expect similar results in the proposed clinical trial. The side effect profile of phentermine+topiramate has been demonstrated to be acceptable in adults and the proposed tests are not more than minimal risk. The alternative treatment approach is standard-of-care lifestyle/behavior modification therapy and/or treatment with orlistat or "off-label" obesity medications. All participants in this study will receive

lifestyle/behavioral modification therapy. Based upon data in adults, it is possible that the benefits of phentermine+topiramate will be additive to the lifestyle/behavioral modification therapy.

14.0 Statistical Considerations

14.1 Data Analysis Plan:

There are three analysis populations planned. Intent-to-treat (ITT) will include any participant randomized according to their treatment assignment. Per-protocol (PP) will include those without major protocol violations. A detailed list of the protocol violations warranting exclusion from the PP analysis will be determined prior to trial commencement. The safety population will include all who receive treatment, according to treatment received.

14.2 Power Analysis:

Based on our preliminary results using a similar meal replacement protocol in adolescents with severe obesity, results of the Berkowitz et al. trial [50] and an adult trial by Wadden et al. (in which 90% achieved ≥5% weight loss during the induction period),[32] we anticipate that at least 70% will achieve the 5% BMI reduction goal and would be randomized. Therefore, we will enroll approximately 100 participants who will start meal replacement therapy, anticipating that 60 (76%) will achieve 5% BMI reduction and be eligible for randomization. Considering a dropout rate *after* randomization as high as 20% (our previous experience with this population has been 10-15%),[60,66] we expect to have complete follow-up data at 12 months post-randomization on ≥67 participants.

Regarding attrition, our group has had strong success in retaining participants. In an unpublished trial with a similar design including a meal replacement run-in period (mentioned in the Research Strategy section), our retention rate following randomization was 85%. We believe the primary reason for the high degree of retention relates to the meal replacement induction phase, which "weeds out" many of the participants most likely to subsequently withdraw. Therefore, based on our track-record and the nature of our trial design, we anticipate having a dropout rate no higher than 20% following randomization (after the meal replacement phase).

The table below presents the power associated with placebo-subtracted BMI reductions ranging from 7-10% between randomization and 12 months based on an overall sample size of 84 (those meeting the BMI reduction goal and ultimately randomized: 42 phentermine/topiramate and 42 placebo). In arriving at these numbers, we considered variability estimates from our pilot

trials[60,66] and the study of Berkowitz et al.,[50] suggesting a conservative standard deviation of approximately 8.9, and a conservative correlation between baseline and follow-up scores of 0.6. We provide the power for a wide range of scenarios including conservative estimates of the potential treatment effect (as low as 7%) and liberal estimates of potential attrition after randomization (as high as 20%).

Power; N=60 (30 per 2 arms) rho=0.6

Difference in change from baseline	7%	8%	9%	10%
Two-sided	96.9%	99.2%	99.8%	100.0%
Two-sided with 10% attrition	95.2%	98.5%	99.7%	99.9%
Two-sided with 20% attrition	92.8%	97.4%	99.3%	99.8%

14.3 Statistical Analysis:

Descriptive analyses of baseline characteristics and outcomes will include means and standard deviations for continuous variables and frequencies for categorical variables. Treatment compliance will also be evaluated. Safety analyses will use the Safety analysis population and will be primarily descriptive reporting the number and percentage of adverse events. All safety outcomes will be evaluated and monitored throughout the trial.

Specific Aim #1: The primary analysis will be conducted using the ITT population to compare the mean BMI percent change from randomization to 52 weeks of follow-up (after the meal replacement period) between the groups, adjusted for BMI at randomization. Confidence intervals (CIs) and P-values will be based on robust variance estimation. Statistical significance will be considered as $p<0.05$. Supportive analyses using the PP population will also be conducted along with consideration of adjustment for residual imbalances between treatment groups after randomization (e.g., in sex). We will also evaluate differences in total body- and visceral-fat, cardiometabolic risk factors, inflammation, oxidative stress, and indices of vascular health over the full length of follow-up for each time point they are measured. The evaluation will be in a similar fashion as the primary outcome wherein analyses will be adjusted for values at randomization. Longitudinal analyses will also be conducted, incorporating the multiple time points these features are measured. Supportive analyses using the PP population will also be conducted. To address the issue of clinical responsiveness, we will describe the proportion of participants with ≥5% BMI reduction and ≥10% BMI reduction (from baseline, pre-meal replacement therapy) at 52 weeks with CIs and P-values based on the Chi-squared test.

Specific Aim #2: The safety analysis will include all participants who receive treatment, according to treatment received. It should be noted that many of these measurements do not have established cut-points indicating a specific safety signal. Therefore, we will evaluate the change from randomization to 52 weeks of follow-up (after the meal replacement period) for heart rate, blood pressure, depression/suicidal ideation, and bone age between the phentermine/topiramate group vs. placebo group, adjusted for each value at randomization. Confidence intervals (CIs) and P-values will be based on robust variance estimation.

Exploratory Aim #3 (Hypothesis-Generating): Metrics of appetite, satiety, and resting/total energy expenditure at 26- and 52 weeks will each be evaluated in a similar fashion as other secondary endpoints wherein analyses will be adjusted for values at randomization and CIs and P-values will use robust variance estimation.

14.4 Data Integrity:

Despite best efforts, it is possible that some data will be missing, which could limit the interpretation and generalizability of results. If the data are missing at random, conditioned on measured covariates, then supplementary analyses adjusting for these covariates will produce unbiased results. For potential missing data mechanisms beyond measured covariates, we will examine the extent to which results may be affected. Imputation techniques will be considered for missing data issues (e.g., multiple imputation). In particular, for the primary analysis we will use multiple imputation techniques for participants on whom we do not have a final measurement. Observations obtained during interim visits will be used for these analyses and additional sensitivity analyses. Secondary endpoints will be handled similarly.

15.0 Health Information and Privacy Compliance

15.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA

Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

15.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

☒ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☒ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☐ Other. Describe:

15.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

We will work with Fairview Research Administration to pull a pool of individuals who have agreed, in their electronic medical record, to learn about potential research studies. The data will be placed in the data shelter so that recruitment letters can be generated and sent to potential participants. Individuals who have indicated that they do not want to be contacted about research will not be approached.

15.4 Approximate number of records required for review: >10,000

15.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☒ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.
Subjects will receive telephone calls and emails regarding the study. The detail of telephone calls that this study requires is outlined in the

consent form. Emails that contain PHI will be sent to the subject/parent via a secure, encrypted manner.

15.6 Explain how the research team has legitimate access to patients/potential participants: This has been explained in other sections of the protocol.

15.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☒ In the data shelter of the Information Exchange (IE)

☒ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☐ In REDCap (recap.ahc.umn.edu)

☒ Store ☐ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu)

☒ Store ☐ Analyze ☐ Share

☐ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☐ Store ☐ Analyze ☐ Share

☐ Other:

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as a tablet or smartphone not previously listed

15.8 Consultants. Vendors. Third Parties:

15.9 Links to identifiable data:
Absolute confidentiality will be maintained. All data will be stored in locked offices and will not be released without consent of participants. Blood samples that are sent to other laboratories will be identified only by study identification number, never by name. Data to be used in scientific presentations or publications will not contain participant identifiers.

15.10 Sharing of Data with Research Team Members:
Study team members will have access to Box and to RedCAP.

15.11 Storage and Disposal of Paper Documents:
All data will be stored in locked offices and will not be released without consent of participants.

16.0 Confidentiality

16.1 Data Security:
Absolute confidentiality will be maintained. All data will be stored in locked offices and will not be released without consent of participant. Data that is collected will be entered into REDCap which is only accessible by the study team. Blood samples that are sent to a Fairview laboratory for analysis will be identified by name and MR number and the results will be posted to the medical record and available to the study participant/parent via MyChart. The samples that are sent to the University of Minnesota Cytokine Reference Laboratory will be identified only by study identification number, and never by name and the results will not be shared with study participants. Data to be used in scientific presentations or publications will not contain participant identifiers.

17.0 Provisions to Monitor the Data to Ensure the Safety of Participants

17.1 Data Integrity Monitoring.

The study will undergo regular monitoring (at least annually) of the facility, staff, and study documents by clinical research associates in the University of Minnesota Clinical Trials Monitoring Service, which specializes in

regulatory compliance for clinical trials associated with the Food and Drug Administration. This service provides regular monitoring of all research-related activities and is offered free of charge through the University of Minnesota Clinical and Translational Science Institute (CTSI). Monitoring of fidelity to the protocol (e.g., protocol deviations) will be performed at each monitoring visit. Monitoring staff will present a summary report to the PI after each monitoring session. If necessary, corrective action plans will be devised and implemented by the PI to address deficiencies.

17.2 Data Safety Monitoring

A data and safety monitoring board (DSMB) will be established, which will include at least one adult obesity medicine specialist or endocrinologist, one pediatric obesity medicine specialist or pediatric endocrinologist, and one biostatistician. DSMB members will not be affiliated with the study. The DSMB will meet every six months, beginning six months after enrollment of the first participant, during the trial to review data and evaluate participant safety. A charter for the DSMB will be developed and approved by its members along with a plan for frequency of data review prior to the commencement of the trial. Review materials for the DSMB will be prepared and presented by the study biostatistician, Dr. Kyle Rudser. A report from each meeting will be sent to the PI and co-investigators advising on the continuation of the study and any suggestions for trial improvement. This report will also be sent to the assigned NIH Program Director and the IRB. An important charge of the DSMB will be to closely monitor fidelity to the protocol (e.g. regularly review the number and types of protocol deviations) as well as monitor the integrity of the data.

17.3 Suicidal Behavior and Suicidal Ideation

Participants (and their parents, if the participant is a minor) will be referred to a mental health professional (MHP) or to their primary care provider if the subject has a PHQ-9 score of >15, any suicidal behavior, or any suicidal ideation of type 4 or 5 on the C-SSRS. They will also be provided with the contact information for the nationwide Suicide and Crisis Lifeline (telephone 988 or 988lifeline.org). If the participant endorses current (in that moment), active suicidal ideation with plan and intent, they will also be referred to the emergency department. Participants (and their parent) will be asked if they feel safe enough to leave the research clinic. If a participant (and their parent) do not feel safe we can help to guide them to the emergency department.

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy: see HIPCO ancillary review

18.2 Access to Participants*:* Please refer to the recruitment section

19.0 Compensation for Research-Related Injury

19.1 Compensation for Research-Related Injury:

Treatment for injuries that result from participating in the research activity will be available. Those treatments include first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to the subject or to their insurance company. Subjects will be encouraged to contact the study team if they think that they have suffered a research related injury.

19.2 Contract Language:

Not applicable.

20.0 Consent Process

20.1 Consent Process (when consent will be obtained):

Assent and parental consent will be obtained by a study investigator or the study coordinator after explaining the entire study in detail, asking the participant and the parent(s)/guardian(s) to explain the purpose, risk and benefits, and other details of the study, and giving the participant and parent(s)/guardian(s) an opportunity to ask questions. A copy of the assent and parental consent form will be given to the participants and parent(s)/guardian(s).

20.2 Waiver or Alteration of Consent Process (when consent will not be obtained):

There is no plan to request a waiver or alteration of the consent process.

20.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):

There is no plan to request a waiver of written/signed documentation of consent.

20.4 Non-English Speaking Participants:

We do not plan on enrolling non-English speaking participants at this time. If we elect to do so at a later time, a revised protocol and translated consents would be sent to the IRB for review and approval.

20.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

This study will enroll subjects who are under the age of 18 and they will be asked to sign an IRB-approved assent form. Their parent(s)/guardian(s) will be asked to sign a parental consent form.

Individuals who sign an assent form but turn 18 during the course of the study will be asked to sign a consent form to indicate that they are still willing to participate in the study. A copy of the consent form will be given to the participant.

20.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

Not applicable

20.7 Adults Unable to Consent:

- Permission:
  Not applicable
- Assent:
  Not applicable
- Dissent:
  Not applicable

21.0 Setting

21.1 Research Sites:

- Center for Pediatric Obesity Medicine
- Delaware Clinical Research Unit
- MHealth Clinics and Surgery Center

21.2 International Research:
Not applicable

22.0 Multi-Site Research

Not applicable

23.0 Coordinating Center Research

Not applicable

24.0 Resources Available

The YWCA Minneapolis is a nonprofit organization founded in 1891 to promote health, education, and gender and racial equity throughout the Twin Cities. YWCA Minneapolis has been cultivating an inclusive and healthy community through a range of programs, classes and workshops. They provide high-quality Racial Justice, Early Childhood Education, Girls & Youth, Health & Wellness and Workforce Development programs that

help build a vibrant, healthy community for all. The YWCA Minneapolis is willing to collaborate with us to include information about research opportunities to 30,000 people who subscribe to their 'Mission in Action e-newsletter. The e-newsletter reaches people involved with the YWCA Minneapolis through their program participants, fitness members, volunteers, donor event attendees and supporters.

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