SMART USE OF MEDICATION FOR THE TREATMENT OF ADOLESCENT SEVERE OBESITY

Protocol Number: 1.0

National Clinical Trial (NCT) Identified Number: NCT04007393

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
8.2	Updates the course of events if PHQ-9 and C-SSRS scores reach a specific threshold	Participant safety

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STATEMENT OF COMPLIANCE

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

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

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

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

1 PROTOCOL SUMMARY

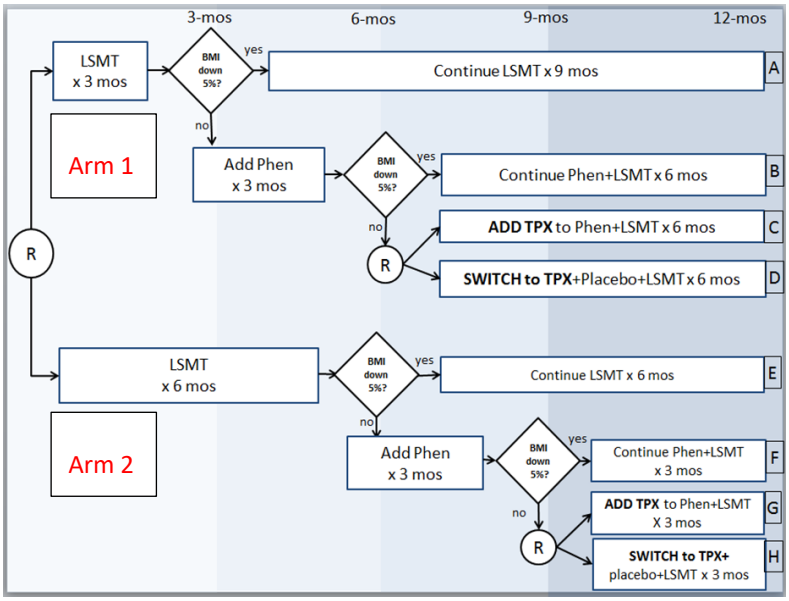
1.1 SYNOPSIS

Title:	SMART Use of Medication for the Treatment of Adolescent Severe Obesity
Study Description:	This is a single site, 2-staged sequential multiple assignment randomized trial (SMART) that will systematically examine: 1) the optimal timing (12- versus 24 weeks) for identifying non-responders to lifestyle modification therapy (LSMT) before starting adjunct pharmacotherapy with phentermine and 2) for non-responders to LSMT+phentermine, the relative effect of adding topiramate to LMST+phentermine versus switching to LSMT+topiramate monotherapy. All participants will receive a total of 48 weeks of intervention. Participant characteristics that differentially predict outcomes and mechanisms that may account for the relative effects will also be examined. We hypothesize that 1) identifying non-responders to LSMT at 12 weeks compared to 24 weeks will result in superior BMI reduction at 48 weeks and 2) for non-responders to LSMT+phentermine, adding topiramate to LSMT+phentermine will be more effective than switching to LSMT+topiramate monotherapy as measured by BMI reduction at 48 weeks.
Objectives:	Primary Objective: Compare the effectiveness of a 12-week versus 24-week response assessment to LSMT before adding adjunct phentermine Secondary Objectives: Among non-responders to LSMT+phentermine, compare the effectiveness of adding topiramate to LSMT+phentermine versus switching to LSMT+topiramate monotherapy.
Endpoints:	Primary Endpoint: Percent change in body mass index (BMI)

	Secondary Endpoints: Changes in body composition, cardiometabolic profile, and quality of life
Study Population:	150 adolescents, ages 12-17 years at study entry, with BMI ≥1.2 times the 95th percentile or BMI ≥35 kg/m^2, and Tanner stage ≥2
Phase:	2
Description of Sites/Facilities Enrolling Participants:	University of Minnesota M Health/Fairview System, Minneapolis, MN Mayo Clinic, Rochester, MN Children's Hospital of Minnesota, Minneapolis, MN Park Nicollet/Health Partners, St. Louis Park, MN Allina Health, Minneapolis, MN Hennepin Health Care, Minneapolis, MN
Description of Sites/Facilities Conducting Research Activities:	University of Minnesota, Minneapolis, MN
Description of Study Intervention:	1. Lifestyle modification therapy (LSMT): dietary and physical activity counseling supported by behavior modification 2. LSMT + Phentermine 15 mg by mouth once daily 3. LSMT + topiramate 100 mg by mouth daily + (phentermine 15 mg or placebo by mouth once daily)
Study Duration:	5 years

Participant Duration: 72 weeks (48 weeks of intervention)

SCHEMA



Key: R: randomization; LSMT: lifestyle modification; Phen: phentermine; TPX: topiramate

Purple: LSMT alone
Blue: LSMT+phentermine open label
Yellow: LSMT+topiramate open label+phentermine/placebo
Green: LSMT+topiramate open label+[hentermine/placebo
Gray: Measurement visit
V: In-person visit
P: Phone visit

	ARM 1				ARM 2			
Screening	V				V			
Randomization + Baseline	V				V			
Week 1								
2	P				P			
3								
4	V				V			
5								
6	P				P			
7								
8	V				V			
9								
10	P				P			
11								
12	V				V			
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39								
40	V				V			
41								
42								
43								
44	V				V			
45								
46								
47								
48	V				V			
55	P				P			
72 Weeks	V				V			

1.2 SCHEDULE OF ACTIVITIES (SOA)

	Screening (-30d - -1d)	Baseline	2-wks (±7d)	4-wks (±10d)	6-wks (±10d)	8-wks (±10d)	10-wks (±10d)	12-wks (±10d)	14-wks (±10d)	16-wks (±10d)	18-wks (±10d)	20-wks (±10d)	22-wks (±10d)	24-wks (±10d)	26-wks (±10d)	28-wks (±10d)	30-wks (±10d)	32-wks (±10d)	34-wks (±10d)	36-wks (±10d	38-wks (±10d)	40-wks (±10d)	42-wks (±10d)	44-wks (±10d)	46-wks (±10d)	48-wks (±10d)	55-wks (±10d)	72-wks (±30d)
Informed consent and assent	X																											
Review inclusion/exclusion criteria	X																											
Review of medical history	X																											
Physical exam	X																											
Tanner stage	X																								X			
Ht, Wt, BP, HR	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X
Demographic questionnaires	X																											
Basic metabolic panel	X							X						X						X					X			
Fasting lipids, glucose, HbA1c, ALT, AST	X							X						X						X					X			
Urine pregnancy test	X	X		X		X		X		X		X		X		X		X		X		X		X	X			
PHQ-9 and C-SSRS	X	X		X		X		X		X		X		X		X		X		X		X		X	X			
ECG	X																								X			
iDXA		X						X						X						X					X			
Bone Age, linear growth velocity		X																							X			
IWQOL-Kids, Social Support for Eating Habits, Social Support for PA, PAQ-A, QEWP-A, RED K5, AEBQ, Dutch Eating Behavior Questionnaire, BRIEF, PROMIS Anxiety		X						X						X						X					X			
ACE-Q teen		X																										
NIH Toolbox		X						X						X						X					X			X
Meal test		X																										
Drug Dispensing (Drug Groups Only)								X						X						X					X			
Weight Loss Goals and Medication Assignment Questions								X						X											X			
Compliance check									X	X	X	X	X	X	X	X		X		X		X		X	X			
AE check and con meds		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X	X
LSMT in person		X		X		X		X		X		X		X		X		X		X		X		X	X			
LSMT by phone			X		X		X		X		X		X		X													

2 INTRODUCTION

2.1 STUDY RATIONALE

Adolescent Severe Obesity: A Serious Disease without an Effective Treatment Algorithm
Severe obesity (age- and sex-specific body mass index (BMI) ≥1.2 times the 95th percentile or ≥35 kg/m^2, whichever is lower)[1] is a complex, chronic and debilitating disease that affects nearly 9% of adolescents in the U.S.[2] and the numbers continue to rise.[3] This disease is associated with significant physiological and psychological morbidity including hypertension,[4] dyslipidemia,[4] pre-diabetes,[5] non-alcoholic fatty liver disease,[6] depression,[7] anxiety[7] and poor quality of life (which is reported to be worse than that of children suffering from cancer).[8] The natural history of untreated adolescent severe obesity is progressive weight gain, such that 88% of 12 year olds with severe obesity become adults with BMI ≥ 35 kg/m^2.[4] Further, the life expectancy of adults with severe obesity is reduced by 7-14 years.[9] Therefore, treating obesity early, in adolescence, is essential for preventing lifelong morbidity and early mortality.

Although metabolic and bariatric surgery is the most effective treatment for adolescent severe obesity, this intervention is not widely accessible[10] and can hardly address the millions of youth affected with severe obesity. In contrast, lifestyle modification therapy (LSMT; dietary and physical activity counseling supported by behavior modification strategies), while readily available, has limited efficacy and durability for adolescent severe obesity.[11-15] Pharmacotherapy represents a potential bridge addressing the large gap between surgery and LSMT. Indeed, adolescent severe obesity treatment guidelines recommend a staged approach that includes LSMT delivered in a progressively more intense manner. If there is no treatment response to LSMT after 3-6 months, adjunct obesity pharmacotherapy is recommended.[16] These recommendations, however, have notable limitations:

1) The recommendation to wait 3-6 months before initiating pharmacotherapy is arbitrary and may contribute to poor outcomes. Given that *early* weight loss success strongly predicts longer-term outcomes in children and adolescents,[17-21] waiting 6-months before initiating "rescue" adjunct pharmacotherapy may be too long for those patients who are struggling to achieve BMI reduction, resulting in patient frustration and treatment drop-out. On the other hand, waiting only 3 months before initiating "rescue" adjunct pharmacotherapy may not be long enough to assess the efficacy of LSMT, potentially resulting in needless exposure to the risks of medication. Because pharmacotherapy is employed long-term, this is of particular importance to adolescents, many of whom are still in phases of physiological and psychological development. Thus, identifying the optimal timing for starting adjunct pharmacotherapy when there is a non-response to LSMT will result in the best outcomes with the least amount of patient risk and waste of resources.

2) There is no evidence or guidance regarding how to manage patients who are non-responsive to first-line pharmacotherapy. For adults with obesity, first-line pharmacotherapy routinely includes combination medications, such as phentermine+topiramate.[22] Importantly, though, these studies of combination medications do not distinguish if a given participant who responds to the combination (e.g. phentermine+topiramate) may have responded just as well to one of the medications or the other (e.g. phentermine or topiramate). In fact, our data indicate that some adolescents with severe obesity have a weight loss response to phentermine and topiramate monotherapy[23-25] that rivals mean outcomes of combination phentermine+topiramate therapy seen in adults. Thus, for patients who are non-responsive to the initial medication, determining the relative effectiveness of *switching* to another medication (e.g.

switching from phentermine to topiramate) versus *adding* a second medication (e.g. phentermine+topiramate) could limit unnecessary medication exposure. Again, this is particularly relevant to the adolescent population where limiting over-medication is highly valued.

3) Treatment responses to LSMT and pharmacotherapy are highly variable and the guidelines do not address this variability. Prior research identified several phenotypic characteristics in youth which moderate responses to LSMT, including baseline BMI, age, sex, ethnic minority status, and binge eating behaviors.[17-19] However, only a few studies examined moderators of pharmacotherapy response and these studies were small, observational in design, and mostly restricted to adults. Nonetheless, these studies showed, for example, that higher baseline hunger predicted greater weight loss with phentermine[26] and phentermine+topiramate.[27] Topiramate has been shown to reduce weight in adults with binge eating disorder who also have obesity,[28,29] perhaps via decreased cravings.[30] Furthermore, several mechanisms by which topiramate and phentermine contribute to weight loss have been proposed including alterations in resting energy expenditure,[31] gastric emptying,[27] appetite hormones,[27] and inhibitory control.[32] Identification of the potential moderators and mediators that differentially contribute to response to a given therapy will allow for tailoring of the interventions to address treatment variability.

Adaptive Interventions for Treating Adolescent Severe Obesity

An adaptive intervention may address many of the uncertainties and limitations of current adolescent severe obesity treatment guidelines. Also called a dynamic treatment regimen, an adaptive intervention is a therapeutic strategy in which the type or dosage of the intervention offered to a patient is personalized based on presenting characteristics and then adjusted over time based on subsequent patient response. The key components of an adaptive intervention include: decision stages with decision rules at each stage, treatment options, and tailoring variables.[33] Adaptive interventions, in contrast to the "one-size-fits-all" approach, have multiple benefits including: helping patients who do not respond to initial treatments, providing direction to treatment that wanes over time due to a patient's changing situation, enhancing adherence by tailoring the treatment, and limiting costs by avoiding unnecessary therapy.[34] Adaptive interventions are particularly effective for the management of chronic conditions that a) have significant heterogeneity in individual response to a given therapy and therefore do not have widely effective therapies and/or b) have widely effective therapies but the therapies are costly or associated with significant risk.[33] Adolescent severe obesity is associated with both of these characteristics; LSMT and pharmacotherapy are not widely effective and response is heterogeneous; on the other end of the treatment spectrum, bariatric surgery for adolescent obesity is widely effective[35] but is not widely accessible due to high costs and limited availability, and poses considerable risk.[10,36]

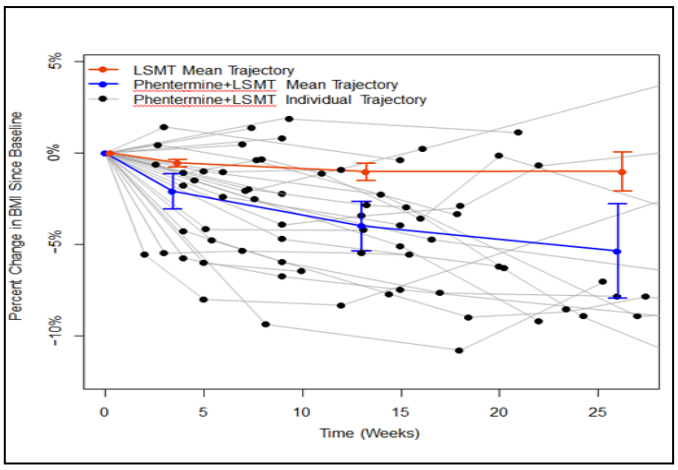
The development of an adolescent severe obesity adaptive intervention that tailors treatment according to a patient's presenting characteristics and that changes over time according to the patient's response (such as degree of BMI reduction) has the potential to dramatically improve outcomes while simultaneously limiting unnecessary exposure to potential side effects of treatment and minimizing waste of clinical resources. **Our goal with this project is to generate data that can be used to inform the development of an adaptive intervention for the treatment of adolescent severe obesity that includes empirically-derived decision rules which address: 1) *when* to start pharmacotherapy, 2) for *which* patients, and 3) *how* to modify the pharmacotherapy based on a patient's profile when there is a sub-optimal response to the initial intervention. Such an adaptive intervention will allow for maximizing outcomes while minimizing risk.** Ultimately, such an algorithm could be integrated into electronic medical record-based clinical decision support tools used by clinicians.

2.2 BACKGROUND

Why Phentermine, Topiramate, and Phentermine+Topiramate?
Currently, orlistat, a lipase inhibitor, is the only medication that is FDA-approved for the indication of obesity in adolescents. Mean BMI reduction with orlistat, however, is modest at <3% in 1 year.[37] Further, because of notable gastrointestinal side effects, orlistat is not often utilized. Because of the limited number of FDA-approved medications for the treatment of obesity in adolescents, other pharmacotherapies utilized for *adult* obesity have been studied for possible use in adolescents. Among the most studied are: metformin, exenatide, topiramate and phentermine. A meta-analysis of several large randomized controlled trials demonstrates that metformin achieves a mean BMI reduction of 3% over 6-12 months.[38] Exenatide, a glucagon-like peptide-1 receptor agonist, also achieves 3% mean BMI reduction as demonstrated in two small pilot randomized controlled studies conducted by our group.[39,40] In contrast, our studies of phentermine[23] and topiramate[25] monotherapy each have modestly superior outcomes. (See below.) Furthermore, combination of phentermine+topiramate (trade name Qsymia) (phentermine 15 mg+topiramate ER 92 mg), although never evaluated in adolescents, is the most effective FDA-approved weight loss medication for adults, producing a mean placebo-subtracted weight loss of 9.8% [(9.3%-10.4%).

Phentermine**,** an amphetamine derivative, was FDA-approved for short-term use in 1959 for the indication of obesity in individuals > 16 years of age. It is the most widely prescribed weight loss medication in the U.S for adults.[41] Phentermine increases norepinephrine activity in the hypothalamus which is posited to decrease hunger. The weight loss achieved with phentermine in adults is on average 3-5%.[42] While expected side effects related to its noradrenergic activity include hypertension and tachycardia, studies have found, in contrast, that blood pressure decreases among adults taking phentermine as a result of weight reduction.[43] Additionally, while there is hypothetical risk of phentermine addiction given its chemical structure, phentermine abuse, dependence, and craving does not occur with phentermine treatment and abrupt discontinuation does not induce withdrawal symptoms (even after decades of treatment at higher than recommended doses).[44] Although there are no randomized controlled studies examining the effect of phentermine for obesity in adolescents, our group published a retrospective chart review detailing the outcomes of phentermine+LSMT for weight reduction in adolescents with severe obesity who were treated in the University of Minnesota Pediatric Weight Management Clinics.[23] We identified 25 patients (mean age 16.1±1.3 years; mean BMI 41.2±6.9 kg/m^2) who were prescribed phentermine 15 mg daily (and no other weight altering medications) in addition to standard of care LSMT and compared them to 274 patients matched for age and BMI range who were prescribed only LSMT. As illustrated in Figure 1 below, phentermine+LSMT compared to LSMT alone was more effective for BMI reduction, with a treatment effect of -2.9% [95%CI(-4.5%, -1.4%), p<0.001) at 3-months and -4.1% [(-7.1%, -1.0%),p=0.009] at 6 months. 40% on phentermine+LSMT compared to 9% on LSMT alone achieved ≥5% BMI reduction at 3-months, and 64% compared to 21%, respectively, achieved ≥5% BMI at 6-months.

Figure 1. Percent Change in BMI at 1-, 3-, and 6-Months with LSMT Only vs Phentermine+LSMT

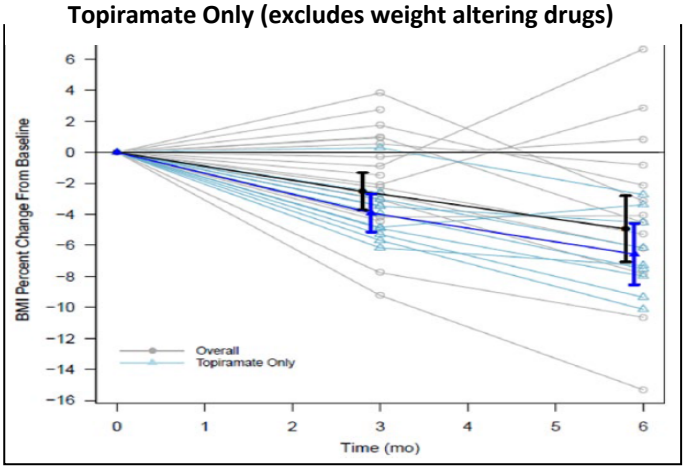


Of important note is the marked variability in BMI reduction with LSMT alone and phentermine+LSMT as seen by the individual trajectories in Figure 1 (to left), where several individuals reduced their BMI by approximately 8-9% at 6-months and others experienced BMI increase. Critically, there were no significant changes in blood pressure in the phentermine+LSMT group. These data suggest that the use of phentermine with LSMT in the clinical setting is well-tolerated and may enhance weight loss in a significant number of adolescents with severe obesity.

Topiramate, an anti-epileptic agent with a well-established safety profile, was FDA-approved in 1999 for the indication of seizures in children ≥2 years of age and is also FDA-approved for migraine prophylaxis in adolescents ≥12 years of age. Topiramate is thought to reduce weight via inhibiting glutamate neurotransmission in the hypothalamus, though the precise mechanism of action is unknown.[45] In adults with obesity, several large randomized controlled studies demonstrate a 4-9% placebo-subtracted weight loss.[46-49] Investigations examining topiramate in youth with obesity are limited to our two published studies described below: a chart review[25] and a pilot randomized, placebo-controlled trial.

The retrospective chart review detailed the outcomes of topiramate+LSMT for weight reduction in adolescents with severe obesity who were treated in the University of Minnesota Pediatric Weight Management Clinic.[25] We identified overall 28 patients (mean age 15.2±2.5 years, mean baseline BMI 46.2±10.3 kg/m^2) who, in addition to LSMT, were prescribed topiramate (most commonly 75 mg daily) for at least 3 months; 11 of the overall 28 were not taking other potentially weight altering medications such as stimulants or metformin. We designated this group as "Topiramate Only" in Figure 2 below.

Figure 2. Percent Change in BMI at 3- and 6-Months with Overall Topiramate (includes weight altering drugs) and Topiramate Only (excludes weight altering drugs)



Topiramate+LSMT was associated with clinically-meaningful BMI reduction: -3.9%[(–5.1%, –2.7%), p<.001] at 3 months and -6.6%[(–8.5%, –4.6%), p,0.001] at 6 months. At 6-months, 67% of the "Topiramate Only" patients achieved ≥5% BMI reduction from baseline. Yet, like with phentermine, there was notable heterogeneity of response as seen in the individual trajectories illustrated in Figure 2, with a few achieving 9-10% BMI reduction and yet others experiencing an increase in BMI. No adverse side effects were reported except for intermittent

paresthesia (tingling in the extremities) in 2 of the 28 patients.

Our group conducted the only randomized, controlled study that has examined the effect of topiramate for adolescent severe obesity. This randomized, double-blind, placebo-controlled pilot clinical trial tested the ability of topiramate to enhance weight loss maintenance following a short-term meal replacement induction phase in adolescents with severe obesity.[24] Participants completed 4 weeks of meal replacement therapy followed by randomization to either 24-weeks of 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. 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]), which was not unexpected considering the pilot nature of the trial and intentionally low dose.

Importantly, our primary focus in this pilot trial was safety, tolerability, and acceptability. At baseline and at last study visit, we measured the Behavior Rating Inventory of Executive Function-Self Report, Cambridge Neuropsychological Test Automated Battery (a computerized test of motor speed, memory, and attention), and the Connors Continuous Performance Test II (a computerized measure of attention and impulsivity). Bone density, geometry, and strength were assessed with peripheral quantitative computed tomography. Bone mineral density was measured by dual energy x-ray absorptiometry (DXA). There were no statistically- or clinically-significant differences between the topiramate and placebo group on any of these measures and none of the participants withdrew from the trial due to experiencing adverse events. The most common adverse event was paresthesia (tingling in the extremities), reported by 25% in the topiramate group and none in the placebo group. These preliminary data suggest that topiramate monotherapy at 75 mg/day is safe and well tolerated but that to achieve clinically significant BMI reduction, a higher dose may be needed. This is consistent with studies of topiramate in adults with obesity, where a dose of at least 100 mg/day is the most effective.[46-49]

Combination of phentermine+topiramate (trade name Qsymia) (phentermine 15 mg+topiramate ER 92 mg), while never evaluated in adolescents, is the most effective FDA-approved weight loss medication for adults. The mean placebo-subtracted weight loss at 1 year is 9.8% [(9.3%-10.4%); p<0·0001], with 70% achieving ≥5% weight loss and 49% achieving ≥10% weight loss.[50] The 2-year extension study showed a durable effect. In addition to weight loss, phentermine+topiramate improved blood pressure, lipid profile, glucose, insulin, HOMA-IR, C-reactive protein, and adiponectin.[18-20] It is noteworthy that a third of the participants did not achieve the 5% weight loss benchmark and half did not achieve the 10% weight loss benchmark. This highlights the heterogeneity of response, even in the adult population.[50] Although this combination medication is indicated as a first line agent in adults, as noted above our prior research demonstrates that some adolescents may achieve weight loss with either phentermine[23] or topiramate[25] monotherapy that rivals the mean outcomes seen in adults from combination therapy. Accordingly, identification of patients who are particularly responsive to monotherapy may obviate the need for combination therapy.

Our unpublished data collected from a retrospective chart review of patients treated with the combination of phentermine and topiramate within our University of Minnesota Pediatric Weight Management Clinic describes the tolerability of this medication in adolescents with severe obesity. 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 mg/day of topiramate. The mean duration of combination treatment was 11.1±10.3 months. We do not report on changes in BMI because many patients were started on either phentermine or topiramate monotherapy followed by the addition of the other medication at a later time-point. Table 1 (below) shows the most commonly-reported side effects. Overall, the incidence was low with a

relatively high rate of resolution. Importantly, only a small percentage of the patients treated with phentermine+topiramate discontinued therapy as a result of side effects. Therefore, these results provide evidence supporting the safety of these medications and demonstrate a high level of acceptability and tolerability in the adolescent population.

Table 1. Adverse Events Observed with Phentermine+Topiramate

Adverse Event Description	Overall % Affected	% Resolution (of those affected)	%Discontinued Due 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	67	1.8
Tachycardia	1.8	0	1.8

In summary, these preliminary data demonstrate that phentermine and topiramate monotherapies are both effective in achieving 4-6% mean BMI reduction in adolescents with severe obesity and that there is notable heterogeneity in response. Further their safety profiles and tolerability in adolescents are acceptable. Although these data suggest that phentermine and topiramate may be equally efficacious, for this protocol we decided to study phentermine as a first-line medication. We made this decision because phentermine is the most widely-prescribed obesity medication for adults in the U.S. and because it is already FDA approved for obesity in adolescents >16 years of age. For non-responders to phentermine, we will test the relative effectiveness of adding topiramate to phentermine versus switching to topiramate monotherapy.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Based upon guidance provided in 45 CFR 46, subpart D sections 401-409 regarding research in children, this proposal poses greater than minimal risk to research participants but provides the prospect of direct benefit to all of the participants. The risk lies mainly in the administration of two medications which are not FDA-approved specifically for the indication of obesity in the targeted population, i.e. in adolescents ages 12-<18 years. In particular, phentermine is FDA-approved for the indication of obesity in people >16 years of age. Topiramate is FDA-approved for the indication of seizures in children ≥2 years of age. Combination phentermine/topiramate is FDA-approved for obesity in people ≥18. Thus, these medications will be used in an off-label manner.

As with any research study, there may be unforeseen risks. A trained interdisciplinary research staff comprised of physicians, scientists, nurses, and study coordinators will carefully guard against all potential risks. Below is a description of the most common potential side effects from the planned interventions and participant interactions:

Lifestyle Modification Therapy (LSMT): Potential risks related to LSMT include sadness or frustration related to difficulty adhering to dietary and activity plans. Participants may also experience injury related to increased physical activity. In our experience, participants tolerate LSMT without difficulty.

Phentermine: The following have been identified as the most common potential adverse events related to phentermine: high blood pressure, tachycardia, palpitations, restlessness, dizziness, insomnia, tremor, headache, dry mouth, diarrhea and constipation. In our experience, the most commonly reported side effect is irritability and rarely do patients discontinue phentermine due to side effects. According to the package insert, the following additional adverse reactions to phentermine have been identified:

- Primary pulmonary hypertension and/or regurgitant cardiac valvular heart disease, ischemic events
- Overstimulation, euphoria, dysphoria, psychosis
- Dryness of mouth, unpleasant taste
- Urticaria
- Impotence, changes in libido
- Risk of abuse and dependence

Topiramate: The following have been identified as the most common potential adverse events related to topiramate: paresthesia, anorexia, weight decrease, dysgeusia, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, difficulty with memory, difficulty with concentration/attention, cognitive problems, confusion, mood problems, fever, infection, flushing. In our experience, the most common side effect is transient irritability and rarely do patients discontinue topiramate due to side effects. According to the package insert, the following additional adverse reactions to topiramate have been identified:

- Acute myopia and secondary angle closure glaucoma
- Oligohidrosis and hyperthermia
- Metabolic acidosis
- Suicidal behavior and ideation
- Fetal toxicity
- Kidney stones
- Seizure precipitation with sudden withdrawal
- Hyperammonemia and encephalopathy
- Hypothermia

Phentermine + Topiramate: The risks of phentermine + topiramate are those noted for phentermine and topiramate used separately as outlined above.

Blood draw: There is a minimal risk of bruising and infection associated with the blood draw. Possible fainting may also occur.

Dual energy x-ray absorptiometry (DXA): The iDXA 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 scan is less than 1% (3 mrem) of that received from natural sources of radiation by a Minnesota resident in one year (300 mrem).

Neuropsychological assessments: Potential risks related to these tests include emotional distress related to thinking about and recording anxiety and depression symptoms and possible "test fatigue."

The anticipated rate of weight loss achieved as a result of study participation should not pose a significant health risk to study participants, though a potential risk of rapid weight loss is gall stone formation.

There is additional risk that participants may not lose weight and as a result, they may experience feelings of disappointment, discouragement, or sadness. However, the proposed SMART is specifically designed to evaluate different treatment options for people who may have difficulty losing weight. Finally, there is a risk of breach of confidentiality associated with the use of data that can be linked back to individuals. We have put in place strong safeguards against such a breach.

The alternative treatment approach is standard-of-care LSMT without pharmacotherapy. We are proposing a higher risk intervention (i.e. addition of pharmacotherapy to LSMT) because LSMT alone is largely ineffective for the targeted population.

2.3.2 KNOWN POTENTIAL BENEFITS

Known potential benefits of participation in this clinical trial include weight reduction and improvement in cardiovascular risk profile. Depending on the treatment arm, participants may decrease their BMI by 5-9% and experience a reduction in blood pressure, fasting glucose and lipids. Further, an advantage of the SMART design is that participants who do not respond to one of the given interventions will have the opportunity to receive a different intervention.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Severe obesity in adolescents is associated with significant morbidity and premature mortality. However, the standard of care treatment, lifestyle modification therapy, is largely ineffective for achieving clinically significant weight loss. Adjunct pharmacotherapy has the potential to improve outcomes in this population, but there are no research-based guidelines that direct when or how to use pharmacotherapy. This study will importantly garner evidence that addresses the optimal time to start adjunct medication and how to proceed if there is a non-response to the initial pharmacological strategy. In all, this research will contribute to the development of effective treatment guidelines which will improve the outcomes of severe obesity in adolescents, an otherwise treatment refractory condition.

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. The side effect profiles of phentermine, topiramate, and phentermine+topiramate are acceptable and the proposed study tests are not more than minimal risk.

Potential risks will be minimized via a comprehensive approach as follows:

- By careful adherence to participant inclusion and exclusion criteria, we will not enroll participants who have contraindications to phentermine and/or topiramate use, or who are at high risk of developing potential side effects from these medications.
- Study medications will be managed by the University of Minnesota Investigational Drug Service Pharmacy. Participants will be instructed to administer the medication(s) under the supervision of a parent/guardian. Participants will be asked to bring their medication bottles with them to study visits so that compliance can be reviewed. Should a participant not bring their study medicine to a visit they will be asked about their compliance. Participants will be reminded about taking their study medication at their phone visits.
- Participants and parent(s)/guardian(s) will be given contact information for the study coordinator and instructions to seek emergency care if needed and call the study coordinator immediately if a serious adverse event is experienced.
- Adverse events will be reviewed at each patient contact. At each in-person contact with the participant and their parent/guardian, adverse events will be assessed by specific questioning and, as appropriate, by physical examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event form. The clinical course of each event will be followed until resolution. Serious adverse events that are still ongoing at the end of the study period will be followed-up to determine the final outcome. Incidental findings will be reported to participant and parent(s)/guardian(s) with appropriate instruction for follow-up as needed.
- Should a participant develop suicidal ideation, the participant will be referred to our pediatric psychologist who is a study co-investigator for further evaluation and management. If a subject should develop suicidal ideation and shares this information with the study coordinator, the pediatric psychologist (a sub-investigator) will be paged so that an evaluation can be undertaken. Should the sub-investigator not be available, then the subject will be referred to an emergency room for management of their condition. The subject's study participation will be halted while the assessment is undertaken.
- Absolute confidentiality will be maintained. All data will be stored in locked offices and will not be released without consent of participants. Data to be used in scientific presentations or publications will not contain participant identifiers.
- The study will undergo regular monitoring by clinical research associates employed by the University of Minnesota Clinical Trials Monitoring Service, which specializes in regulatory issues related to IND under the authority of the FDA.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Compare the effectiveness of a 3-month versus 6-month response	**1°:** change from baseline to 12-mos:	Percent change in BMI is a clinically relevant

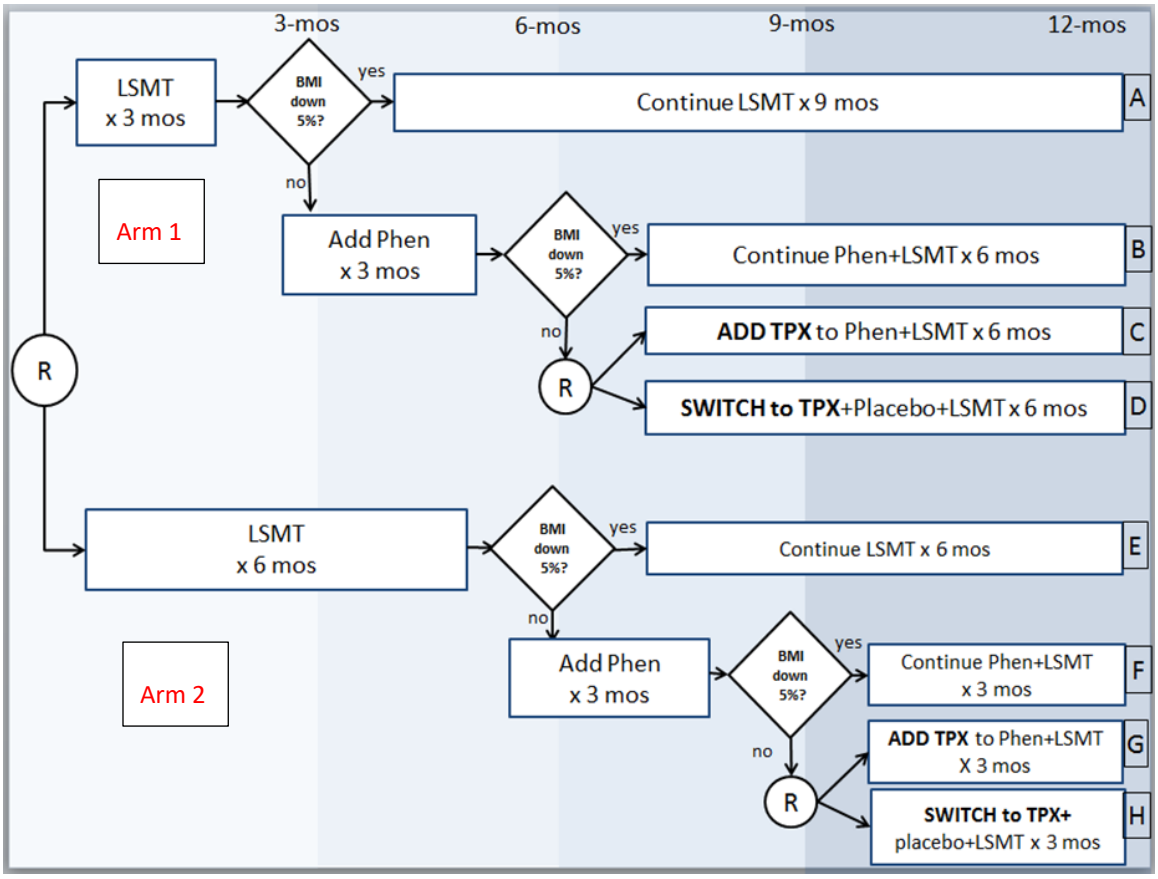
OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
assessment to LSMT before adding adjunct phentermine	Percent of body mass index (BMI)	measure of pediatric obesity interventions
	2°: change from baseline to 12-mos: Body composition • total percent body fat, visceral fat, and lean muscle mass Cardiometabolic profile • blood pressure, heart rate, total-, LDL-, HDL-cholesterol, triglycerides, glucose, hemoglobin A1c, ALT, AST Quality of life • IWQOL-Kids	Changes in body composition, cardiometabolic profile, and quality of life are clinically relevant measures of pediatric obesity interventions
Secondary		
Among non-responders to LSMT+phentermine, compare the effectiveness of adding topiramate to LSMT+phentermine versus switching to LSMT+topiramate monotherapy	**1°:** from baseline to 12-mos: Percent change in body mass index (BMI)	Percent change in BMI is a clinically relevant measure of pediatric obesity interventions
	2°: change from baseline to 12-mos: Body composition • total percent body fat, visceral fat, and lean muscle mass Cardiometabolic profile • blood pressure, heart rate, total-, LDL-, HDL-cholesterol, triglycerides, glucose, hemoglobin A1c, ALT, AST Quality of life • IWQOL - Kids	Changes in body composition, cardiometabolic profile, and quality of life are clinically relevant measures of pediatric obesity interventions
Tertiary/Exploratory	Moderators and Mediators	Justification for Moderators and Mediators
To consider more deeply tailored adaptive interventions, explore moderators (that may explain for whom the intervention works) and	Demographics/Environment • Age • Sex • Race/ethnicity	Demographics, social environment, Tanner stage, eating behaviors neuropsychological

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
mediators (that may explain how the intervention works) that may differentially contribute to response to a given sequence of intervention.	• Home address • Total combined family income • Parents' level of education • Parents' employment status • Food security screen • Social Support for Eating Habits • Social Support for Exercise • ACE-Q Teen Tanner stage Physical activity • Physical Activity Questionnaire for Adolescents – PAQ-A Eating behaviors • 7-day diet diary • Questionnaire of Eating and Weight Patterns – Adolescent (binge eating behavior measure) • Adult Eating Behavior Questionnaire • Reward-Based Eating Drive Dutch Eating Behavior Questionnaire (eating restraint, emotional eating, and external eating measure)Neuropsychological function • Behavior Rating Inventory of Executive Function – Self Report (BRIEF-SR) (executive function measure) • NIH Tool Box (cognition battery) • PROMIS Pediatric Short Form v 2.0 – Anxiety 8a Resting metabolic rate Standardized meal test	function, and standardized meal tests may moderate endpoints. Changes in diet, physical activity, and resting metabolic rate may mediate endpoints (i.e. uncover mechanisms that account for response to interventions).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This will be a single site, phase 2, 2-stage sequential multiple assignment randomized trial (SMART) designed to evaluate in 150 adolescents with severe obesity: 1) the relative effectiveness of a 12-week versus 24-week response assessment to LSMT before starting adjunct phentermine; and 2) if there is a non-response to adjunct phentermine, the relative effectiveness of adding topiramate to phentermine vs switching to topiramate monotherapy. All participants will undergo a first 1:1 double blind randomization to LSMT with a response assessment at either 12 weeks or 24 weeks. We will define a positive response as ≥5% decrease in BMI from baseline for both time points; non-response is <5% decrease in BMI. LSMT responders will continue with LSMT for the remainder of the trial (36 weeks for Arm 1 and 24 weeks for Arm 2). LSMT *non-responders* will be started on phentermine and then undergo a second response assessment after 12 weeks of therapy. Responders to LSMT+phentermine will continue with LSMT+phentermine for the remainder of the trial and non-responders to LSMT+phentermine will undergo a second 1:1 double blind placebo controlled randomization to either adding topiramate to LSMT+phentermine or *switching* to LSMT+topiramate(+placebo). All participants will receive a total of 48 weeks of intervention and have a follow-up visit 24 weeks after the end of intervention, for a total of 72 weeks (18 months) of participation.



4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Sequential Multiple Assignment Randomized Trials (SMARTs) were developed explicitly for constructing adaptive interventions.[34,51] SMARTs are an experimental design ideally suited to obtain data that inform the decision rules that specify whether, how, when, and based on which measures, to alter the intensity, dosage, type, or delivery of treatment(s) at critical decision points in the course of care. A SMART involves multiple intervention stages; each stage corresponds to one of the critical decisions involved in an adaptive intervention. Each participant moves through the multiple stages, and at each stage the participant may be randomly (re)assigned to one of several intervention options. As in standard intervention trials, the randomization creates the opportunity to make valid causal inferences concerning the relative effectiveness of the intervention options without having to make unverifiable assumptions.[34] The SMART design for weight loss intervention studies has the ability to address some of the limitations of the "one size fits all" approach by experimentally testing competing interventions for non-responders.[33] Thus, utilizing a SMART design in the context of interventions for adolescent severe obesity can provide critical experimental data regarding when is the optimal time for initiating adjunct treatment (i.e. medication) and what type of "stepped care" intervention strategy is most effective for non-responders to the initial intervention.

Rationale for BMI reduction benchmarks:

LSMT: Based on data collected from the POWER registry, which examines outcomes of LSMT in the context of multicomponent pediatric weight management clinics, we identified that ≥5% BMI reduction (compared to 2%, 3%, and 4%) over both 3 months and 6 months has the best balance of positive and negative predictive values for 12-month outcomes (Tables 2 below).[52] That is, for example, 95% of patients who do not achieve ≥5% BMI by 6 months, will not achieve ≥5% BMI at 12 months. Thus, in using the ≥5% BMI reduction by 6 months benchmark, we are operating under the assumption that the majority who do not achieve this benchmark would benefit from adjunct pharmacotherapy and only 5% who achieve this benchmark would be treated with pharmacotherapy perhaps unnecessarily.

Table 2. Selected 3- and 6-month % BMI reduction cut-offs for early weight loss as predictors of ≥5% BMI reduction at 12 month visits. Data are presented with the 95% CI provided in parentheses.

X% BMI decrease at 3 months	Positive predictive value (%)	Negative predictive value (%)		X% BMI decrease at 6 months	Positive predictive value (%)	Negative predictive value (%)
≥2%	38.6 (26.0,52.4)	97.4 (91.0,99.7)		≥2%	53.3 (43.4,63.0)	98.3 (95.0,99.6)
≥3%	44.2 (29.1,60.1)	94.6 (87.8,98.2)		≥3%	61.1 (50.3,71.2)	97.4 (93.9,99.1)
≥4%	51.9 (31.9,71.3)	90.7 (83.6,95.5)		≥4%	70.8 (58.9,81.0)	95.7 (91.9,98.0)
≥5%	52.6 (28.9,75.6)	87.9 (80.6,93.2)		≥5%	86.0 (74.2,93.7)	95.0 (91.3,97.5)

Pharmacotherapy: First, the FDA recommends a placebo-subtracted BMI reduction of ≥5% as a benchmark for determining effectiveness of weight loss medications for pediatric use.[53,54] Second, studies of obesity pharmacotherapy for adults indicate that if a patient does not achieve a 5% weight reduction benchmark, it is unlikely that the patient will achieve and sustain clinically significant weight loss with continued treatment.[55]

4.3 JUSTIFICATION FOR DOSE

The phentermine dose we selected is 15 mg orally every morning. This dose was chosen because 1) 15 mg is the dose of phentermine in the most effective strength of combination phentermine+topiramate and 2) while higher doses of phentermine monotherapy are available (i.e., 30 mg and 37.5 mg), this medication has never been studied in the adolescent population in a systematic fashion beyond 2 weeks. Therefore we are operating conservatively.

Topiramate will be started at 25 mg orally once daily in the morning for 7 days, then increased to 50 mg daily for the next 7 days, then 75 mg daily for the next 7 days, then 100 mg daily thereafter through week 48. At the end of week 48, topiramate dose will be decreased to 50 mg once daily for 7 days, then discontinued. This dose of 100 mg daily was chosen because 1) the topiramate portion in the most effective strength of combination phentermine+topiramate is 92 mg extended-release and 100 mg approximates this, 2) our randomized, placebo-controlled study of topiramate 75 mg daily following a meal replacement induction phase did not result in clinically significant weight loss, so we believe a higher dose is warranted, and 3) the side effects of topiramate are dose dependent and most commonly emerge above a dose of 100 mg daily, therefore we did not want to exceed 100 mg daily.[46] At the end of the study, those on topiramate will be weaned off as follows: 50 mg daily for 7 days, then discontinue. (Phentermine does not require weaning before discontinuation.)

4.4 END OF STUDY DEFINITION

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally. This will be week 72.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Provision of signed and dated informed assent form
2. Provision of signed and dated informed consent from at least 1 legal parent/guardian
3. Stated willingness to comply with all study procedures and availability for the duration of the study
4. BMI ≥1.2 times the 95th percentile or BMI ≥35 kg/m^2, whichever is lower
5. Tanner stage ≥2
6. Male or female, aged 12-17 at time of consenting
7. For females of reproductive potential: when sexually active, agreement to use highly effective contraception (oral contraceptive pill, IUD, or implant) during study participation
8. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner

5.2 EXCLUSION CRITERIA

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

- Contraindications to phentermine or topiramate use according to package inserts, including:
  - history of glaucoma
  - current or recent (<14 days) use of monoamine oxidase inhibitor
  - known hypersensitivity to sympathomimetic amines
  - current pregnancy, plans to become pregnant, or if sexually active, refusal to use 2 forms of birth control
  - history of cardiac disease, including coronary artery disease, clinically significant congenital heart disease, stroke, clinically significant cardiac arrhythmias, heart failure, or uncontrolled hypertension
- Blood pressure, for ages 13 and older of $\geq$130/80 on 3 separate occasions and for age 12 $\geq$ 95th percentile on 3 separate occasions
- Heart rate ≥120 bpm on 3 separate occasions
- Diabetes (type 1 or 2)
- Presence of cardiac pacemaker
- Current or recent (<6 months prior to enrollment) use of weight loss medication(s)
- Current use of weight-altering medication(s) (e.g., atypical antipsychotic, metformin) unless dose has been stable for past 6 months. Individuals on an SSRI will need to be on stable dose for 3 months.
- Current use of other sympathomimetic amine such as ADHD stimulants
- Seizure disorder (other than infantile febrile seizure)
- Previous bariatric surgery
- Recent initiation or change in dose (<3 months prior to enrollment) of anti-hypertensive or lipid medication(s)
- Tobacco use
- History of or current diagnosis of schizophrenia, psychosis, mania, chemical dependency
- Unstable depression or anxiety that has required hospitalization in the past year
- Any history of suicide attempt
- Suicidal ideation or self-harm within 3 months prior to enrollment
- PHQ-9 score ≥15
- Suicidal ideation of type 4 or 5 on C-SSRS in the past 3 months
- Bicarbonate <18 mmol/L
- Creatinine >1.2 mg/dL
- History of cholelithiasis
- History of nephrolithiasis
- Untreated thyroid disorder
- Hyperthyroidism
- Breastfeeding

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

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

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a modifiable factor may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The target population is 150 adolescents, ages 12-17 years at study entry, with BMI ≥1.2 times the 95th percentile or BMI ≥35 kg/m^2, and Tanner stage ≥2. We expect to enroll 4.2 participants per month over 36 months for a total of 150 participants.

Recruitment will be executed via our partnerships with members of the MN Pediatric Obesity Consortium which include University of MN, Mayo Clinic, Rochester, Park Nicollet, and Children's Hospital of MN.
Strategies to recruit will include:

1) mailing letters to the homes of potentially-eligible participants from participating sites (based on our prior experience, we anticipate that we will be able to *enroll* 2-4% of potentially-eligible participants who receive letters in the M Health Fairview system). Procedures for identifying eligible patients will be outlined in MOP and will require local IRB approval from each site.

   Participating sites may include:
   - M Health/Fairview System
   - Mayo Clinic
   - Children's Hospitals and Clinics of Minnesota
   - Park Nicollet/Health Partners
   - Allina Health
   - Hennepin Health Care

Recruitment Site	Demographics	Number of Adolescents with Severe Obesity
University of Minnesota	12-18 year old with severe obesity	>3,000
Children's Hospitals and Clinics of Minnesota	12-18 year old with severe obesity	>7,000
Mayo	Contingency	
Park Nicollet/Health Partners	Contingency	
Allina	Contingency	
Hennepin Health Care	Contingency	

2) directly approaching potentially-eligible patients in the clinics *where co-investigators work*. Only appropriately certified staff will approach potential participants.

Participating clinics will include:

- University of MN Pediatric Weight Management Clinics
- Mayo Clinic, Rochester Pediatric Endocrinology
- Children's Hospitals and Clinics of Minnesota Endocrinology clinic
- International Diabetes Center, Park Nicollet

3) sending MyChart messages to potentially-eligible patients in the MHealth EPIC system.

Although multiple sites will be used for recruiting participants, ALL STUDY ACITIVITES will be conducted at the University of Minnesota

Participant retention will be achieved via the following:

- Exceptional "customer service"
- Providing parking and all medications and supplies
- Up to $1150 in compensation for completion of entire study. Compensation will be given to the participant. We will use a compensation schedule that rewards compliance with attending the multiple study visits.

Compensation plan:

The compensation for this study is designed to compensate participant time and inconvenience for participation in tasks and completion of LSMT visits. The total compensation a participant can receive is $1150. A break down is provided below:

1) Screening: $25
2) 5 long assessment visits (Baseline, 12-, 24-, 36-, 48-weeks): $100 each = $500
3) 19 LSMT visits: $10 each = $190
4) Week-72 follow-up visit = $50

Sub-total: $765; to be dispensed at each noted visit in the form of ClinCards

Incentive for Completion Compensation
≥10 LSMT visits - $50 bonus
≥15 LSMT visits - $100 bonus
≥ 18 LSMT visits - $200 bonus
≥19 LSMT + last big visit (week 48) - $385 bonus

Incentive for completion compensation will be dispensed at the end of the study, week 72. For participants who drop out earlier, compensation will be mailed to their house.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study interventions include the following:
1. phentermine
2. topiramate + placebo
3. topiramate + phentermine
5. lifestyle modification therapy

Phentermine

Phentermine: FDA-approved for indication of short-term treatment of obesity in individuals who are 17 years of age or older. This study will be using phentermine in a non-FDA approved manner given age of target population and duration of treatment.

Phentermine**,** an amphetamine derivative, was FDA-approved for short-term use in 1959 for the indication of obesity in individuals > 16 years of age. It is the most widely prescribed weight loss medication in the U.S for adults.[41] Phentermine increases norepinephrine activity in the hypothalamus which is posited to decrease hunger. The weight loss achieved with phentermine in adults is on average 3-5%.[42] While expected side effects related to its noradrenergic activity include hypertension and tachycardia, studies have found, in contrast, that blood pressure decreases among adults taking phentermine as a result of weight reduction.[43] Additionally, while there is hypothetical risk of phentermine addiction given its chemical structure, phentermine abuse, dependence, and craving does not occur with phentermine treatment and abrupt discontinuation does not induce withdrawal symptoms (even after decades of treatment at higher than recommended doses).[44] Although there are no randomized controlled studies examining the effect of phentermine for obesity in adolescents, our group published a chart review of phentermine outcomes from our pediatric weight management clinics.[23]

CLASSES
Centrally-Acting Antiobesity Products

DEA CLASS

Rx, schedule IV

DESCRIPTION
Oral sympathomimetic amine pharmacologically similar to amphetamines
Used for short-term (a few weeks) treatment of exogenous obesity in patients 17 years and older; use generally not recommended by guidelines due to lack of longer-term health benefits
Not recommended for long-term use; there is abuse and addiction potential

COMMON BRAND NAMES
Adipex-P, Atti-Plex P, Atti-Plex P Spansule, Fastin, Lomaira, Pro-Fast, Tara-8

HOW SUPPLIED
Adipex-P/Atti-Plex P Spansule/Fastin/Phentermine Hydrochloride/Pro-Fast Oral Cap: 15mg, 18.75mg, 30mg, 37.5mg
Adipex-P/Atti-Plex P/Lomaira/Phentermine Hydrochloride/Pro-Fast/Tara-8 Oral Tab: 8mg, 37.5mg

DOSAGE & INDICATIONS
For the short-term (i.e., a few weeks) treatment of exogenous obesity.

Oral dosage (phentermine hydrochloride 15 mg or more per oral capsule or tablet; e.g., Adipex-P)
Adults and Adolescents 17 years and older
15 to 37.5 mg PO once per day as a single dose every morning before breakfast or approximately 2 hours after breakfast. Some tablets with a score may be divided, with 18.75 mg (half-tablet) given in the morning and the other half-tablet later in the day (but not in the late evening), if needed. For some patients 18.75 mg PO once daily is sufficient. Geriatric patients may require a lower dosage.

INTENDED USE: For patients with a BMI of 30 kg/m2 or more or those with a BMI 27 kg/m2 or more in the presence of at least 1 other weight-related risk factor (e.g., controlled hypertension, diabetes mellitus, or dyslipidemia). Use as monotherapy; for short-term use only.[46595] According to the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) Obesity Clinical Practice Guidelines, short-term pharmacotherapy, such as with phentermine, has not been shown to produce longer-term health benefits in obese and overweight patients and cannot be generally recommended.[62881]

Oral dosage (phentermine 8 mg tablet; e.g., Lomaira)
Adults and Adolescents 17 years and older
8 mg PO 3 times per day, 30 minutes before meals. Dosing selection in geriatric patients should be cautious, usually starting at the low end of the dosing range. One-half of the usual dose (i.e., 4 mg PO 3 times per day) may be used for patients not requiring the full dose. Use the lowest effective dose. Avoid late evening dosing due to the potential for insomnia. INTENDED USE: For patients with a BMI 30 kg/m2 or more or those with a BMI 27 kg/m2 or more in the presence of at least 1 other weight-related risk factor (e.g., controlled hypertension, diabetes mellitus, or dyslipidemia). Use as monotherapy; for short-term use only. According to the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) Obesity Clinical Practice Guidelines, short-term pharmacotherapy, such as with phentermine, has not been shown to produce longer-term health benefits in obese and overweight patients and cannot be generally recommended.

MAXIMUM DOSAGE

Adults
37.5 mg/day PO.
Elderly
37.5 mg/day PO. May require reduced dosage compared to younger adults.
Adolescents
> 16 years: 37.5 mg/day PO.
<= 16 years: Safety and efficacy have not been established.
Children
Safety and efficacy have not been established.

DOSING CONSIDERATIONS
Hepatic Impairment
The effects of hepatic impairment on phentermine and its metabolites are unknown.

Renal Impairment
Phentermine 8 mg tablets (e.g., Lomaira):
Use with caution. Specific guidelines for dosage adjustments in renal impairment are not available. Based on the reported excretion of phentermine in urine, exposure increases can be expected in patients with renal impairment.

Phentermine 15 mg and 30 mg tablets (generic manufacturers):
eGFR greater than 29 mL/min/1.73 m2: No dosage adjustment required.
eGFR 15 to 29 mL/min/1.73 m2: Do not exceed 15 mg/day PO.
eGFR less than 15 mL/min/1.73 m2: Avoid use.

Phentermine HCl 37.5 mg tablets and capsules equivalent to 30 mg of phentermine base (e.g., Adipex-P):
eGFR greater than 29 mL/min/1.73 m2: No dosage adjustment required.
eGFR 15 to 29 mL/min/1.73 m2: Do not exceed 15 mg/day PO.
eGFR less than 15 mL/min/1.73 m2: Avoid use.

Intermittent hemodialysis
Some manufacturers (e.g., Adipex-P) recommend avoiding the drug in patients with end-stage renal disease requiring dialysis. There are no recommendations for Lomaira in patients receiving dialysis.

ADMINISTRATION
For storage information, see the specific product information within the How supplied section.

Oral Administration
Phentermine hydrochloride oral capsules or tablets (Adipex-P or equivalent 15 mg to 37.5 mg products):
The usual dose is administered daily before breakfast or 1 to 2 hours after breakfast.
Tablets may contain a score to allow daily dose to be divided in half and administered before meals or 1 to 2 hours after meals.
Avoid late evening administration because of the possibility of insomnia.

Phentermine hydrochloride oral tablets (Lomaira 8 mg tablet or an equivalent 8 mg product):
The usual dose is administered three times per day, 30 minutes before meals.

The tablets are scored for administration of one-half of the usual dosage for patients not requiring the full dose.
Avoid late evening administration because of the possibility of insomnia.

STORAGE
Generic:
- Protect from moisture
- Store at controlled room temperature (between 68 and 77 degrees F)
Adipex-P:
- Store at controlled room temperature (between 68 and 77 degrees F)
Atti-Plex P :
- Store at controlled room temperature (between 68 and 77 degrees F)
Atti-Plex P Spansule :
- Store at controlled room temperature (between 68 and 77 degrees F)
Fastin:
- Protect from moisture
- Store at controlled room temperature (between 68 and 77 degrees F)
Ionamin:
- Store at 77 degrees F; excursions permitted to 59-86 degrees F
Lomaira :
- Store at controlled room temperature (between 68 and 77 degrees F)
Pro-Fast:
- Discard product if it contains particulate matter, is cloudy, or discolored
- Protect from light
- Store at controlled room temperature (between 68 and 77 degrees F)
- Store in original container
Suprenza:
- Store at controlled room temperature (between 68 and 77 degrees F)

CONTRAINDICATIONS / PRECAUTIONS
General Information

Phentermine is contraindicated for use in any patient with a prior history of sympathomimetic amine hypersensitivity or idiosyncratic reaction to sympathomimetic amines.
Angina, cardiac arrhythmias, cardiac disease, coronary artery disease, heart failure, hypertension, pulmonary hypertension, stroke, valvular heart disease

Phentermine is contraindicated in patients with a history of cardiac disease, including coronary artery disease, stroke, cardiac arrhythmias, heart failure, or uncontrolled hypertension. Patients with controlled hypertension should receive phentermine with caution and with close monitoring of blood pressure. Valvular heart disease has been reported in women receiving the combination of fenfluramine and phentermine; the safety and efficacy of combination therapy with phentermine and any other drug products for weight loss, including selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, fluvoxamine, paroxetine), have not been established. Therefore, coadministration of these drug products for weight loss is not recommended. Further, primary pulmonary hypertension (PPH) has been reported to occur in patients receiving a combination of phentermine with fenfluramine or dexfenfluramine. The possibility of an association between the use of phentermine alone and PPH or valvular heart disease cannot be ruled out. The initial symptom of PPH is usually dyspnea. Other initial

symptoms include: angina pectoris, syncope, or lower extremity edema. Patients should be advised to report immediately any deterioration in exercise tolerance. Treatment should be discontinued in patients who develop new, unexplained symptoms of dyspnea, angina pectoris, syncope, or lower extremity edema.

Hyperthyroidism, thyroid disease
Because phentermine is a sympathomimetic agent, it is contraindicated in patients with hyperthyroidism. It should also be used with caution in patients with thyroid disease.

MAOI therapy
Phentermine is contraindicated for use during or within 14 days following MAOI therapy because of the risk of hypertensive crisis.

Anxiety, insomnia, mania, psychosis, schizophrenia
Phentermine is contraindicated in patients with agitated states. Psychiatric conditions that may be associated with agitated states include but are not limited to anxiety disorders, schizophrenia, psychosis, and mania. Use with caution in such patients and monitor closely for changes in moods and behaviors or for insomnia. Symptoms of chronic intoxication include insomnia, irritability, change in personality, and psychotic symptoms that may be clinically indistinguishable from other psychotic disorders, like schizophrenia.

Driving or operating machinery, ethanol ingestion
The use of phentermine may cause dizziness, mask signs of fatigue or the need for rest, or impair the ability of a patient to participate in activities that require mental alertness. Advise patients to use caution when driving or operating machinery, or performing other tasks that require mental alertness until they are aware of how therapy will affect their mental and/or motor performance. In general, ethanol ingestion may aggravate these effects or cause an adverse drug reaction. Advise patients to avoid alcohol while taking phentermine.

Diabetes mellitus
Use phentermine cautiously in patients with diabetes mellitus. Insulin or other antidiabetic medication requirements may be altered in these patients when using phentermine during weight loss and due to altered dietary regimens. Patients should monitor their blood glucose regularly and follow the recommendations of their health care provider.
Anorexia nervosa, substance abuse

Appetite suppressant therapy is not recommended for use in those patients with a history of anorexia nervosa or other eating disorders. Use of phentermine is contraindicated in patients with a known history of drug or substance abuse. Phentermine is chemically and pharmacologically related to the amphetamines which have been extensively abused. The possibility of abuse of phentermine should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. The least amount reasonable should be prescribed or dispensed at one time in order to limit the potential for overuse or drug diversion.
Abrupt discontinuation

Abrupt discontinuation of phentermine after prolonged high doses may result in severe mental depression or extreme fatigue; sleep EEG changes have also been noted. Gradual withdrawal of therapy

is recommended. If immediate discontinuation is medically necessary, careful monitoring and symptom management is warranted.
Closed-angle glaucoma

Phentermine is contraindicated in patients with closed-angle glaucoma. Sympathetic stimulation that occurs with phentermine can block aqueous outflow and raise intraocular pressure. Patients should be advised to report any new visual disturbance since an ophthalmic evaluation may be needed.
Dialysis, geriatric, renal disease, renal failure, renal impairment

The debilitated or geriatric patient may be more susceptible to the CNS and sympathomimetic side effects of phentermine; use with caution in geriatric patients. Patients with renal impairment or renal disease may also be more susceptible to side effects resulting from increased systemic exposure to phentermine. Caution is recommended when administering phentermine to patients with mild to moderate renal impairment, although no dosage adjustments are required. Some manufacturers (e.g., Adipex-P) recommend a reduced daily maximum dose in severe renal impairment (eGFR 15 to 29 mL/min/1.73 m2) and avoiding phentermine in patients with renal failure, including those receiving dialysis.

Pregnancy
Phentermine products are contraindicated for use during human pregnancy, as are many anorexiants used for weight loss. Safe use of phentermine during pregnancy has not been established; there is no known indication for use of phentermine during pregnancy. Phentermine should not be taken by women who may become pregnant unless, in the opinion of the physician, the potential benefits outweigh the possible hazards.
Breast-feeding

Phentermine is contraindicated during breast-feeding. It is not known whether phentermine and its metabolites are excreted in breast milk; however, because of the potential for serious adverse effects in the nursing infants, breast-feeding while taking phentermine is not recommended.
Children, infants

Safety and effectiveness of phentermine in children have not been established. Phentermine is not recommended for children or adolescents 16 years of age and under. There is no established use of phentermine in infants.
Surgery

The use of inhalational anesthetics during surgery may sensitize the myocardium to the effects of sympathomimetic drugs. Because of this, and its effects on blood pressure, in general, phentermine should be discontinued several days prior to surgery.

ADVERSE REACTIONS
Severe
cardiac valvulopathy / Delayed / 0-1.0
pulmonary hypertension / Delayed / 0-1.0
Moderate

euphoria / Early / 1.0-10.0
dysphoria / Early / 1.0-10.0

constipation / Delayed / 1.0-10.0
psychosis / Early / 0-1.0
tolerance / Delayed / 10.0
dyspnea / Early / Incidence not known
sinus tachycardia / Rapid / Incidence not known
palpitations / Early / Incidence not known
hypertension / Early / Incidence not known
peripheral edema / Delayed / Incidence not known
angina / Early / Incidence not known
impotence (erectile dysfunction) / Delayed / Incidence not known
psychological dependence / Delayed / Incidence not known
withdrawal / Early / Incidence not known
physiological dependence / Delayed / Incidence not known

Mild
restlessness / Early / 1.0-10.0
insomnia / Early / 1.0-10.0
headache / Early / 1.0-10.0
dizziness / Early / 1.0-10.0
tremor / Early / 1.0-10.0
xerostomia / Early / 1.0-10.0
diarrhea / Early / 1.0-10.0
nausea / Early / 1.0-10.0
dysgeusia / Early / 1.0-10.0
urticaria / Rapid / 0-1.0
syncope / Early / Incidence not known
libido decrease / Delayed / Incidence not known
libido increase / Delayed / Incidence not known

TOPIRAMATE

Topiramate is an antiepileptic medication that is FDA-approved for the indication of seizures in patients ≥2years of age and migraine prophylaxis ins patients ≥12years of age. This study will be using topiramate in a non-FDA approved manner given the indication for obesity.

TOPAMAXâ(topiramate) TABLETS, for oral use, Initial U.S. Approval:1996

INDICATIONS AND USAGE----------TOPAMAX is indicated for:·Epilepsy:initialmonotherapyinpatients≥2yearsofagewithpartialonsetorprimarygeneralizedtonic-clonic seizures (1.1); adjunctive therapy for adults and pediatric patients (2to 16years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and for patients ≥2years of age with seizures associated with Lennox-Gastaut syndrome (1.2)·Prophylaxisofmigraineinpatients12yearsofageandolder(1.3)

DOSAGE AND ADMINISTRATION----------TOPAMAX initial dose, titration, and recommended maintenance dose varies by indication and age group. See Full Prescribing Information for recommended dosage, and dosing considerations in patients with renal impairment, geriatric patients, and patients undergoing hemodialysis(2.1, 2.2, 2.3, 2.4, 2.5, 2.6)

DOSAGE FORMS AND STRENGTHS----------Tablets: 25mg, 50mg, 100mg, and 200mg (3)·Sprinkle Capsules: 15mg and 25mg (3)

CONTRAINDICATIONS----------None(4)

WARNINGS AND PRECAUTIONS----------
·Acutemyopiaandsecondaryangleclosureglaucoma:canleadtopermanentvisualloss;discontinue TOPAMAX as soon as possible(5.1)·Visualfielddefects:consider discontinuation of TOPAMAX (5.2) Oligohidrosis and hyperthermia: monitor decreased sweating and increased body temperature, especially in pediatric patients (5.3)Metabolic acidosis: baseline and periodic measurement of serum bicarbonate is recommended; consider dose reduction or discontinuation of TOPAMAX if clinically appropriate (5.4) Suicidal behavior and ideation: antiepileptic drugs increase the risk of suicidal behavior or ideation (5.5) Cognitive/neuropsychiatric adverse reactions: use caution when operating machinery including cars; depression and mood problems may occur (5.6) Fetal Toxicity: use during pregnancy can cause cleft lip and/or palate and being small for gestational age(5.7) Withdrawal of AEDs: withdraw TOPAMAX gradually (5.8)·Hyperammonemia/encephalopathy: measure ammonia if encephalopathic symptoms occur(5.9)·Kidneystones:avoidusewithothercarbonicanhydraseinhibitors,drugscausingmetabolicacidosis, or in patients on a ketogenic diet(5.10)·Hypothermiahasbeenreportedwithandwithouthyperammonemia during topiramate treatment with concomitant valproic acid use (5.11)

ADVERSE REACTIONS----------Epilepsy: Most common (≥10% more frequent than placebo or low-dose TOPAMAX) adverse reactions in adult and pediatric patients were: paresthesia, anorexia, weight loss, speech disorders/related speech problems, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, abnormal vision and fever(6.1)Migraine: Most common (≥5% more frequent than placebo) adverse reactions in adult and pediatric patients were: paresthesia, anorexia, weight loss, difficulty with memory, taste perversion, diarrhea, hypoesthesia, nausea, abdominal pain and upper respiratory tract infection(6.1)To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc.at 1-800-JANSSEN (1-800-526-7736)or FDA at 1-800-FDA-1088 orwww.fda.gov/medwatch.

DRUGINTERACTIONS----------Oral contraceptives: decreased contraceptive efficacy and increased breakthrough bleeding, especially at doses greater than 200mg/day (7.3) Monitor lithium levels if lithium is used with high-dose TOPAMAX(7.4)

PHENTERMINE+TOPIRAMATE

Phentermine+Topiramate extended-release is trade named Qsymia.™ It is FDA-approved for the indication of chronic treatment of obesity in patients ≥18 years. In a non-FDA approved manner, this study will be using phentermine capsules and topiramate tablets (immediate release) in combination to simulate Qsymia.

The most effective dose of Qsymia is phentermine 15 mg + topiramate extended release 92 mg daily. This study will use phentermine 15 mg + topiramate 100 mg daily.

QSYMIA (phentermine and topiramate extended-release) capsules, for oral use, CIV Initial U.S. Approval: 2012

INDICATIONS AND USAGE---------- Qsymia is a combination of phentermine, a sympathomimetic amine anorectic, and topiramate extended-release, an antiepileptic drug, indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: • 30 kg/m2 or greater (obese) (1) or • 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia (1) Limitations of Use: • The effect of Qsymia on cardiovascular morbidity and mortality has not been established (1). • The safety and effectiveness of Qsymia in combination with other products intended for weight loss, including prescription and over-the-counter drugs, and herbal preparations, have not been established (1).

DOSAGE AND ADMINISTRATION----------• Take once daily in morning. Avoid evening dose to prevent insomnia (2.1). • Recommended dose: Qsymia 3.75 mg/23 mg (phentermine 3.75 mg/topiramate 23 mg extended-release) daily for 14 days; then increase to 7.5 mg/46 mg daily (2.1). • Discontinue or escalate dose (as described) if 3% weight loss is not achieved after 12 weeks on 7.5 mg/46 mg dose (2.1). • Discontinue Qsymia if 5% weight loss is not achieved after 12 weeks on maximum daily dose of 15 mg/92 mg (2.1). • Discontinue 15 mg/92 mg dose gradually (as described) to prevent possible seizure (2.1). • Do not exceed 7.5 mg/46mg dose for patients with moderate or severe renal impairment or patients with moderate hepatic impairment (2.2, 2.3).

DOSAGE FORMS AND STRENGTHS---------- Capsules: (phentermine mg/topiramate mg extended-release) • 3.75 mg/23 mg (3) • 7.5 mg/46 mg (3) • 11.25 mg/69 mg (3) • 15 mg/92 mg (3)

CONTRAINDICATIONS----------Pregnancy (4) • Glaucoma (4) • Hyperthyroidism (4) • During or within 14 days of taking monoamine oxidase inhibitors known hypersensitivity or idiosyncrasy to sympathomimetic amines (4)

WARNINGS AND PRECAUTIONS----------• Fetal Toxicity: Females of reproductive potential: Obtain negative pregnancy test before treatment and monthly thereafter; use effective contraception. Qsymia is available through a limited program under a Risk Evaluation and Mitigation Strategy (REMS) (5.1). • Increase in Heart Rate: Monitor heart rate in all patients, especially those with cardiac or cerebrovascular disease (5.2). • Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue Qysmia if symptoms develop (5.3). • Acute Myopia and Secondary Angle Closure Glaucoma: Discontinue Qsymia (5.4). • Mood and Sleep Disorders: Consider dose reduction or withdrawal for clinically significant or persistent symptoms (5.5). • Cognitive Impairment: May cause disturbances in attention or memory. Caution patients about operating automobiles or hazardous machinery when starting treatment (5.6). • Metabolic Acidosis: Measure electrolytes before/during treatment (5.7). • Elevated Creatinine: Measure creatinine before/during treatment (5.8). • Use of Antidiabetic Medications: Weight loss may cause hypoglycemia. Measure serum glucose before/during treatment

ADVERSE REACTIONS---------- Most common adverse reactions (incidence greater than or equal to 5%) are: paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth (6.1). To report SUSPECTED ADVERSE REACTIONS, contact VIVUS Inc., at 1-888-998-4887 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS---------- • Oral contraceptives: Altered exposure may cause irregular bleeding but not increased risk of pregnancy. Advise patients not to discontinue oral contraceptives if spotting occurs (7.2). • CNS depressants including alcohol: Potentiate CNS depressant effects. Avoid

concomitant use of alcohol (7.3) • Non-potassium sparing diuretics: May potentiate hypokalemia. Measure potassium before/during treatment (7.4)

USE IN SPECIFIC POPULATIONS----------• Nursing Mothers: Discontinue drug or nursing (8.3). • Pediatric Use: Safety and effectiveness not established and use not recommended (8.4).

PLACEBO

A placebo capsule will be formulated by the University of Minnesota Investigational Drug Service Pharmacy such that it is identical in appearance to phentermine 15 mg

LIFESTYLE MODIFICATON THERAPY

throughout the entirety of the 48-week intervention phase. Each session will last 30-60 minutes. A trained study coordinator (a registered dietician or someone trained by our registered dietician) will deliver this therapy which consists of counseling using education, goal setting, and barrier reduction. Topics covered will include:

1. Getting Started: Calories, Tracking
2. Healthy Food Choices, Reducing High Fat, Added Sugar Foods
3. Setting Goals and Portions
4. Changing the quality of your diet, Volumetrics
5. Purposeful Activity
6. Quick and Easy Meals
7. Problem Solving
8. Food Cues, Eating Patterns
9. Emotional Eating
10. Accurate Tracking
11. Eating Away from Home
12. Unhelpful Thoughts
13. Structured Menus, Role of Protein
14. Social Cues
15. Managing Stress
16. Slips, Relapse Prevention
17. Long-term Physical Activity, Overcoming Obstacles
18. High-Risk Situations, Keys to Success
19. Motivation
20. Looking to the Future: Long-term Plans

For participants 14 years of age or younger, phone session will be conducted with parent/guardian. For participants 16 years and older the phone session will be conducted with the participant. For participants who are 15 years old, target of counseling will be at discretion of study coordinator.

6.1.2 DOSING AND ADMINISTRATION.

All participants will receive LSMT every 2weeks from baseline through week 28 and every 4 weeks from week 28 through week 48.

Phentermine will be started only if a participant does not lose 5% of BMI after 12 or 24 weeks of LSMT, depending on if randomly assigned to Arm 1 or Arm 2. If phentermine is started it will be started at 15 mg by mouth every morning. No dose escalation will be required. Participants will take phentermine 15 mg every morning for 12 weeks at which time there will be an assessment of weight loss:

- Participants who achieve 5% or more BMI reduction after 12 weeks of phentermine will continue phentermine 15 mg every morning for the remainder of the study (through week 48)
- Participants who do NOT achieve at least 5% BMI reduction after 12 weeks of phentermine will be re-randomized 1:1 to either topiramate+phentermine OR topiramate+placebo
    - Topiramate dosing:
        -25 mg every morning for first 7 days, then
        -50 mg every morning for next 7 days, then
        -75 mg every morning for next 7 days, then
        -100 mg every morning through week 48
        - at end of week 48, taper off: 50 mg every morning for 7 days, then discontinue
    - Phentermine dosing:
        -15 mg every morning OR placebo every morning

For participants who do not tolerate phentermine 15 mg daily because of adverse events, the dose will be reduced to 8 mg daily for the remainder of the study. If the participant does not tolerate 8 mg daily, the medication will be discontinued but the participant will remain in the study.

For participants who do not tolerate topiramate 100 mg daily, the dose will be decreased to 50 mg daily. If the participant does not tolerate 50 mg daily, the medication will be discontinued but the participant will continue in the study. If topiramate adverse event is fatigue or cognitive difficulties, changing timing of dose from am to pm will be tried before decreasing dose.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The study intervention and control product will be prepared by the University of Minnesota Investigational Drug Service Pharmacy. Study drug/placebo will be dispensed from the IDS. Study drug reconciliation/chain of custody will be performed on a regular basis to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug dispensation case report form.

At the completion of the study, there will be a final reconciliation of drug consumed and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to the destruction of unused study drug.

Drug destroyed on site will be documented in the study files and completed per the IDS standard operating procedures.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Phentermine capsules are gray and yellow. These will be used for the unblinded portion of the study.

For the blinded portion of the study comparing topiramate+phentermine vs topiramate+placebo, each participant will receive 2 pills: 1 topiramate round white tablet (100 mg daily after up titration – see dosing section for up titration) and 1 encapsulated pill that will contain either phentermine 15 mg or placebo. The encapsulated pills will be identical in appearance.

6.2.3 PRODUCT STORAGE AND STABILITY

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

6.2.4 PREPARATION

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Because this study uses a SMART design, each participant will undergo at least 1 and possibly 2 randomizations during the course of the study.

ALL participants will undergo the first randomization at baseline. Using permuted blocks of size 2, 4, or 6, each participant will be randomized 1:1 to either the 12-week (Arm 1) or 24-week (Arm 2) response assessment to LSMT. This randomization will be double-blinded. Specifically, all participants will be blinded to their treatment arm for the duration of the study interventions, i.e. up until 48 weeks. To achieve this, each participant will start LSMT at baseline without knowledge of the exact timing of the weight loss response assessment. Participants will only be informed that they will be assigned, by chance, to a varying duration of LSMT and that phentermine may be added at some point to aid in weight management. The study coordinator who is delivering the LSMT will also be blinded to participant arm assignment but only *up until 12-weeks*.

The second randomization includes only those participants who are non-responders to LSMT+phentermine (i.e. do not achieve 5% BMI reduction after 12 weeks of phentermine 15 mg daily). Using permuted blocks of size 2, 4, or 6, each non-responder to LSMT+phentermine will be re-randomized 1:1 to either LSMT+topiramate+phentermine or LSMT+topiramate+placebo. Participants and study coordinators will both be blinded to phentermine/placebo. The topiramate will be open label.

Randomization and treatment decision rules will be built into Redcap.

A randomization number will be assigned at baseline starting with SM001 and numbered sequentially. Randomization codes will be maintained at the University of Minnesota Investigational Drug Service

Pharmacy. The PI will be responsible for determining when individual treatment assignments should be un-blinded (e.g., safety issues).

A different study coordinator who is not delivering the interventions will be responsible for all assessments, the results of which will not be made known to the coordinator delivering the interventions.

6.4 STUDY INTERVENTION COMPLIANCE

LSMT adherence will be assessed by asking participants about their eating habits and their activities.

Study drug compliance will be assessed at all phone and in-person visits. Participants will be asked to bring in their medication bottles to their in-person visits so that compliance can be measured. Participants who forget to bring their medication bottles will be asked about their compliance with taking the study medication.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. Concomitant medication(s) status will be collected at the baseline visit. Changes in concomitant medication(s) will be assessed during follow-up visits. Should a participant start treatment with a sympathomimetic amine, monoamine oxidase inhibitor, or any other medication that is contraindicated with phentermine or topiramate, the study medication will be discontinued and the participant will remain in the study if deemed medically stable otherwise.

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

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

In the event that a participant has a *serious* adverse event that is deemed study-related by the lead investigator for medical safety or DSMB, the participant will be required to immediately discontinue the study medication.

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

- Date, time, duration and dose of study medication, and reason for discontinuation of study medication including relevant participant history, symptoms, physical examination findings, laboratory values, EKG, and imaging.
- The relevant symptoms, physical examination findings, laboratory values, EKG, and imaging will be monitored until resolution.
- Any interventions used to manage/treat the reason for discontinuation of study medication

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants will be informed that they may withdraw from the study at any time and for any reason. The overall study may be stopped at any time at the request of the PI and/or the DSMB.

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

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study medication for 7 days

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

Participants who are taking topiramate and wish to withdraw from the study will be instructed to wean off the medication as follows: 50 mg daily for 7 days, then discontinue.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for more than 24 weeks and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Informed consent and assent process Appropriate designees will discuss study participation with interested participants and their parents at which time the initial consent and assent discussion will be conducted. Assent and consent will be obtained by the study coordinator after explaining the entire study in detail, asking the participant and the parent(s)/guardian(s) to explain the purpose, risks and benefits, and other details of the study, and giving the participant and parent(s)/guardian(s) an opportunity to ask questions. A copy of the assent and consent form will be given to the participants and parent(s)/guardian(s). Participants who turn 18 years of age during course of study will be re-consented.

Review inclusion/exclusion criteria Trained study personnel will review inclusion and exclusion criteria with parent/guardian and participant at the time of study screening

Physical exam and Tanner stage A board-certified pediatrician will perform all physical examinations. All Tanner staging will be conducted by individuals trained in assessing Tanner stage.

Anthropometrics: 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.

Blood pressure and heart rate: Blood pressure measurements will be obtained manually on the same arm and according to standard procedures. Individual cuff size will be determined by measuring the arm circumference midway between the acromial process and the bony olecranon. Sitting blood pressure and heart rate will be measured after the participant has been resting quietly without legs crossed for 10 minutes. Measurements will be made three consecutive times (3-minute intervals). The final two of three independent measurements will be averaged.

Dual Energy X-ray Absorptiometry (DXA): Total percent body fat, visceral fat, lean muscle mass, and bone mineral density will be determined by dual energy x-ray absorptiometry (iDXA, GE Healthcare) using standard operating procedures.

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

Meal Test: A standardized meal test will measure appetite, satiety, hormones and gastric emptying. After having fasted for ≥12 hours, participants will consume (within five minutes) a fixed-size, single-item breakfast protein drink. Fasting (pre-meal) and serial postprandial (15-, 30-, 60-, and 90-, and 120-minutes) plasma concentrations of glucose, insulin, leptin, ghrelin, peptide YY (PYY), GLP-1, glucose-dependent insulinotropic polypeptide (GIP), amylin, pancreatic polypeptide, and cholecystokinin will be measured (will require insertion of a polyethylene catheter in an antecubital vein), along with ratings on 15-cm visual analog scales from "not at all" to "extremely" for appetite, satiety, desire to eat, and nausea. This method, which we are currently using in a different trial (R01-DK105953), has been validated for use in appetite research71 and was recently utilized by Sysko et al.72 in a study of adolescents with severe obesity. We will calculate the area-under-the-curve (AUC) for all the biomarkers and visual analog scale results for the entire standardized meal test.

Demographics/Environmental Assessment:

- Age
- Sex
- Race/ethnicity
- Home address
- Total combined family income
- Parents' level of education
- Parents' employment status
- Food security screen
- Social Support for Eating Habits
- Social Support for Exercise
- ACE-Q Teen (Adverse Childhood Event)

Physical Activity and Eating Behavior Assessment

- Physical Activity Questionnaire for Adolescents – PAQ-A
- 7-day diet diary
- Questionnaire of Eating and Weight Patterns – Adolescent (binge eating behavior measure)
- Adult Eating Behavior Questionnaire
- Reward Based Eating Drive Scale X5 (hedonic eating)
- Dutch Eating Behavior Questionnaire (eating restraint, emotional eating, and external eating measure)

Neuropsychological Function

- Behavior Rating Inventory of Executive Function – Self Report (BRIEF-SR) (executive function measure)
- NIH Tool Box (cognition battery)
- PROMIS Pediatric Short Form v 2.0 – Anxiety Symptoms 8a
- Impact of Weight on Quality of Life – Kids (IWQOL-Kids)

Satisfaction with weight loss goals and medication assignment: Participants who are first starting Phentermine (at either 12 or 24 weeks, depending on randomization) will be asked about how they feel about starting phentermine at this point in the study. At week 48, participants will also be asked about their weight loss. The questions will vary based on their treatment assignment.

Optional Biobank

For participants who opt in to participating in biobanking, the biospecimens (stool, blood, and urine samples) will be stored indefinitely for future analysis (-80 degrees C) in a locked -80 freezers at the 717 Delaware Street Building, in a room that is secured by coded access. All specimens are identified by unique study ID only. A blood sample for genetic analysis will be collected from subjects who have consented to participate in the optional biobank component of the trial.

8.2 SAFETY AND OTHER ASSESSMENTS

The PI, Claudia Fox, MD, MPH, is a board-certified pediatrician and bariatrician with 10 years of experience in treating children and adolescents with severe obesity. She has been utilizing obesity pharmacotherapy, including phentermine, topiramate, and phentermine+topiramate, in her clinical practice for approximately 8 years and is very familiar with the potential side effects. The other study team members are also experts in the medical care of children, including a pediatric psychologist and pediatric endocrinologists. Additionally, we will utilize a Medical Safety Director and an independent DSMB comprised of a biostatistician, a pediatric cardiologist, and a psychiatrist. See DSMP for details of DSMB.

Potential risks will be minimized via a comprehensive approach as follows:

- By careful adherence to participant inclusion and exclusion criteria, we will not enroll participants who have contraindications to phentermine and/or topiramate use, or who are at high risk of developing potential side effects from these medications.
- Study medications will be managed by the University of Minnesota Investigational Drug Service Pharmacy. Participants will be instructed to administer the medication(s) under the supervision of a parent/guardian.
- Participants and parent(s)/guardian(s) will be given contact information for the study coordinator and instructions to seek emergency care if needed and call the study coordinator immediately if a serious adverse event is experienced
- AEs will be reviewed at each in person contact (i.e. monthly) and by phone at Week 55 with the participant and their parent/guardian, adverse events will be assessed by specific questioning and, as appropriate, by physical examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event form. The clinical course of each event will be followed until resolution. Serious adverse events that

are still ongoing at the end of the study period will be followed-up to determine the final outcome. Incidental findings will be reported to participant and parent(s)/guardian(s) with appropriate instruction for follow-up as needed.

- Absolute confidentiality will be maintained. All data will be stored in locked offices and will not be released without consent of participants. Data to be used in scientific presentations or publications will not contain participant identifiers.
- The study will undergo regular monitoring by clinical research associates employed by the University of Minnesota Clinical Trials Monitoring Service, which specializes in regulatory issues related to IND under the authority of the FDA.

Medical history: (screening visit) potential participant and parent/legal guardian will be interviewed to identify chronic medical conditions, past surgical history, past medical history, and past psychiatric history including prior diagnoses of depression, anxiety, ADHD/ADD, learning disability, and chemical dependency

Medical record review: (screening visit) if potential participant is recruited from Fairview/MHealth, electronic health record will be reviewed for further identification of exclusion criteria

Blood pressure and heart rate: (screening, baseline, monthly x 12, Week 72) Blood pressure measurements will be obtained manually on the same arm and according to standard procedures. Individual cuff size will be determined by measuring the arm circumference midway between the acromial process and the bony olecranon. Sitting blood pressure and heart rate will be measured after the participant has been resting quietly without legs crossed for 10 minutes. Measurements will be made three consecutive times (3-minute intervals). The final two of three independent measurements will be averaged.

- Potential participant will not be enrolled if BP is ≥95th percentile on 3 separate occasions. If participant develops hypertension in range requiring pharmacotherapy (i.e. BP ≥95th percentile with symptoms or ≥99th percentile) during study, he/she will be referred to cardiology for evaluation and management. Participant will remain on study medication as long as blood pressure can be controlled.
- Potential participant will not be enrolled if HR is ≥120 bpm on 3 separate occasions. If participant develops tachycardia (i.e. HR ≥120 bpm) during the study he/she will be referred to cardiology for evaluation and management. Participant will remain on medication as long as heart rate can be controlled.

Physical exam: (screening) including assessment of general appearance, thyroid gland, cardiovascular system, respiratory system, abdomen, gross neurological system. Abnormalities will be recorded.

Tanner stage: (screening and 48-week visit) Pubertal development will be assessed with Tanner staging in accordance with stages 1-5. 48-weekTanner staging is not required if participant is Tanner 5 at screening visit.

Lab tests: (screening, 12-, 24-, 36-, and 48-wks) basic metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose)

- If bicarbonate drops below 18 mmol/L or creatinine increases >0.3mg/dL from baseline during the course of the study, a repeat measurement will be obtained

within 48 hours. If abnormalities persist, participant will be referred to pediatric nephrology for evaluation and management.

Urine pregnancy test (for girls): (screening, baseline, then every 4 wks through week 48) We will require all sexually active females to confirm use of at least 1 form of effective contraception (i.e. oral contraceptive, IUD, or implant).

- Participant will be withdrawn from study with a positive test
- Informing participant's parent/guardian of a positive test will be according to MN State statute

ECG: (screening and 48-wks) 12-lead ECG will be obtained with an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals.

- Clinically significant ECG recordings will be reviewed by pediatric cardiology for evaluation and management

Bone Age: (baseline and 48-wks) An x-ray of left hand and wrist will be performed at baseline and at 12-months. X-rays will be interpreted by experienced radiologists. Participants for whom bone age indicates that epiphyses are fused will not need repeat bone age at 48-wks.

DXA: (baseline, 12-, 24-, 36- and 48-wks) bone mineral density will be determined by dual energy x-ray absorptiometry (iDXA, GE Healthcare) using standard operating procedures.

NIH Tool Box of Cognitive Function (baseline, 12-, 24-, 36-, 48-, and 72 weeks): Measures neurocognitive function, including attention, memory and psychomotor speed

Depression and Suicide Screening (screening, baseline, then every 4 wks through week 48): The PHQ-9 and C-SSRS (Columbia-Suicide Severity Rating Scale) will measure depression and suicidality and the results will be reviewed by a staff member while the participant is still present at the visit.. A subject will be referred to a Mental Health Professional (MHP) or primary care provider if he/she has:

- A PHQ-9 score ≥ 10
- Any suicidal behavior
- 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.

A referral to a Mental Health Professional (MHP) or primary care provider should also be made if in the opinion of the Investigator it is necessary for the safety of the participant. If a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the participant, at the discretion of the MHP or primary care provider, should be continued in the trial on randomized therapy.

Review of AEs: (baseline, 4-, 8-, 12-, 16-, 20-, 24-, 28-, 32-, 36-, 40-, 44-, 48- and 55-wks) A check list of the following possible side effects will be reviewed: paresthesia (tingling in hands, feet, face), dysgeusia (altered taste sensation), constipation, diarrhea, nausea, dry mouth, depressed mood, agitation, suicidal ideation or self-injurious behavior, acute change in visual acuity, acute eye pain, difficulty falling asleep/insomnia, sleepiness/fatigue, difficulty focusing or concentrating, memory problem, headaches, dizziness, heart palpitations, shortness of breath at rest, chest pain, fainting, swelling of lower extremity, severe side/flank or back pain, cola- or pink/red-colored urine.

Inter-current Illnesses/Medications: (every participant contact starting at 2-wks and going through 72-wks) Participants will be queried about any inter-current illnesses, clinic or hospital visits, or medication changes.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

• An AE 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 AE can be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the AE definition include:

• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
• A CLAE: a clinical abnormal laboratory finding which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
• Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction.
• Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent.
• A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.

Events NOT meeting the AE definition

• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product.

Note: pre-existing conditions should be recorded as Medical history/Concomitant illness.

• Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

- Results in death
- Is life-threatening

  The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  • Hospitalization signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

  Note:

  §Hospitalizations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs.

  §Hospitaladmissionsforsurgicalprocedures,plannedbeforetrialinclusion,arenot considered AEs or SAEs.
- Results in persistent disability/incapacity

  • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

  • This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Important medical event:

  • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 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

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (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.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

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

Expected AEs include but are not limited to:
Signs: metabolic acidosis, hypertension, tachycardia, hyperthermia
Symptoms: paresthesia (tingling in hands, feet, face), dysgeusia (altered taste sensation), constipation, diarrhea, nausea, dry mouth, depressed mood, agitation, suicidal ideation or self-injurious behavior, acute change in visual acuity, acute eye pain, difficulty falling asleep/insomnia, sleepiness/fatigue, difficulty focusing or concentrating, memory problem, headaches, dizziness, heart palpitations, shortness of breath at rest, chest pain, fainting, swelling of lower extremity, severe side/flank or back pain, cola- or pink/red-colored urine

8.3.4 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 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the study staff will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The following AE's will be solicited using a checklist at 12-, 16-, 20-, 24-, 28-, 32-, 36-, 40-, 44-, 48-, and 55-weeks: paresthesia (tingling in hands, feet, face), dysgeusia (altered taste sensation), constipation, diarrhea, nausea, dry mouth, depressed mood, agitation, suicidal ideation or self-injurious behavior, acute change in visual acuity, acute eye pain, difficulty falling asleep/insomnia, sleepiness/fatigue, difficulty focusing or concentrating, memory problem, headaches, dizziness, heart palpitations, shortness of breath at rest, chest pain, fainting, swelling of lower extremity, severe side/flank or back pain, cola- or pink/red-colored urine, any interval change in physical or mental health diagnoses including visits to a health care provider or episode requiring change in normal routine or medication use including over the counter medication

The following AE's will be assessed by physical exam and urine test at screening, baseline, 4-, 8-, 12-, 16-, 20-, 24-, 28-, 32-, 36-, 40-, 44-, and 48-weeks: hypertension, tachycardia, and pregnancy

The following AE's will be assessed at screening, 12-, 24-, 36-, and 48-weeks: basic metabolic panel for bicarbonate <18 mmol/L and creatinine >0.3 mg/dL increase from baseline.

8.3.5 ADVERSE EVENT REPORTING

A report of all AEs will be made available to the DSMB for review quarterly.

Non-serious AEs will be recorded and are available to any review entity (i.e. UM IRB, NIH, FDA) upon request.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study staff will immediately report to the PI any serious adverse event, whether or not considered study intervention related. All serious adverse events (SAEs) will be followed until satisfactory resolution or until the PI deems the event to be chronic or the participant is stable.

The PI will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the PI's initial receipt of the information. The PI will additionally report all SAEs to the University of MN IRB within 5 business days and to the DSMB within 30 days.

In addition, the PI must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the PI determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Incidental findings that are deemed clinically significant by the PI will be reported to the participant with appropriate instruction for follow-up as indicated with participant's primary doctor.

8.3.8 EVENTS OF SPECIAL INTEREST

Not Applicable

8.3.9 REPORTING OF PREGNANCY

In the event that a participant becomes pregnant during the course of the trial, the following procedures will ensue:

Trial product will be discontinued
Participant will be removed from trial
FDA, IRB and DSMB will be notified within 10 days
Informing parent/guardian will occur in accordance with MN State statute re Minor's Consent for Health Care

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The PI will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB), FDA and DSMB. The UP report will include the following information:

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

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB, FDA and DSMB within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB, FDA, and DSMB within 30 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.]

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

If unanticipated problems are identified and are severe enough to warrant a change to the 'Risks' section of the protocol, then the consent should be updated and subjects who are enrolled should be told about the event and allowed to make a determination about whether or not they want to remain in

the study. If they do want to remain in the study, the subject would sign the revised consent and a note in the subject file should address that the revised risks were discussed.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Aim 1

- Primary Efficacy Endpoint(s): Participants first randomized to the 12-week vs 24-week response assessment to LSMT will have a greater percent decrease in BMI measured at 48-weeks.

- Secondary Efficacy Endpoint(s): Participants first randomized to the 12-week vs 24-week response assessment to LSMT will have a greater improvement in body composition (percent body fat, visceral fat, lean body mass), cardiometabolic profile (blood pressure, fasting lipids, fasting glucose, hemoglobin A1c, ALT, AST) and quality of life measured at 48-weeks.

Aim 2

- Primary Efficacy Endpoint(s): Among non-responders to LSMT+phentermine, those randomized to adding topiramate versus switching to topiramate monotherapy will have a greater percent decrease in BMI measured at 48-weeks.

- Secondary Efficacy Endpoint(s): Among non-responders to LSMT+phentermine, those randomized to adding topiramate versus switching to topiramate monotherapy will have a greater improvement in body composition (percent body fat, visceral fat, lean body mass), cardiometabolic profile (blood pressure, fasting lipids, fasting glucose, hemoglobin A1c, ALT, AST) and quality of life measured at 48-weeks.

Aim 3

- Participants' response to LSMT, phentermine, topiramate and phentermine+topiramate will vary according to demographics, environment, eating behaviors, neuropsychological function, and meal test appetite hormones
- Outcomes of LSMT, phentermine, topiramate, and phentermine+topiramate will be mediated by changes in diet, physical activity, and resting energy expenditure

9.2 SAMPLE SIZE DETERMINATION

The proposed trial is powered for a main effect analysis of the effect of the 12-week assessment of LSMT compared to the 24-week assessment of LSMT where the outcome is percent change in BMI from baseline measured 48 weeks after baseline. We emphasize that the power calculation for **Aim 1** is equivalent to a standard two-arm intervention trial. Power for Aim 1 is shown in Table 1 below which assumes a total sample size of 150 participants under different assumptions concerning the standard deviation of the percent change in BMI and the difference between treatment groups. For Aim 1, the analysis will pool all participants randomized to the 12-week assessment compared to the 24-week assessment, so all 150 participants will be included in this analysis. We considered a difference between treatment groups of 4

percentage points to be of interest.[22] Hypothesizing the within-group standard deviation for the outcome (percent change in BMI at 48 weeks) is challenging as most prior work has not estimated the variability within an adaptive intervention strategy. There is likely to be significant variability in the response to any single intervention (or combination of interventions). However, in this study, participants who do not respond to a particular intervention are given a different intervention. Because participants change interventions until they respond to one, we would expect the variability in the outcome to be less than a study in which non-responding participants must continue with a single intervention. In our randomized trial of topiramate[24] and our observational data on phentermine,[23] the standard deviation of the percent change in BMI ranged from 3.5% to 6.3%. A large, national study of LSMT showed a standard deviation of the percent change in BMI of 7.1%.[52] These studies likely over-estimate the standard deviation we would expect in this study. Therefore, we believe that a within group standard deviation between 3% and 7% in this study is reasonable (and conservative). Table 1 indicates we have sufficient power to detect a 4% difference and even reasonable power across many scenarios to detect smaller changes.

Table 1. Aim 1 Power Calculation

	Difference in BMI Percent Change		
Within Group SD	**3%**	**4%**	**5%**
3%	100	100	100
5%	95.4	99.8	100
7%	74.1	93.5	99.1

We also show sufficient power to test our hypotheses for **Aim 2** (Table 2). We emphasize that the power calculation for Aim 2 is equivalent to a standard two-arm intervention trial conducted among the population of non-responders to LSMT+phentermine. For this analysis, we provide power calculations under the assumption that the proportion of participants who will be randomized to second-stage treatments (i.e. the non-responders to phentermine+LSMT) is approximately 50% of the total sample. We estimated this percentage based on the assumption that in the first-stage randomization to the 12-week and 24-week assessment of LSMT, 85% and 80%, respectively, will NOT achieve ≥5% BMI reduction[52] and, therefore, will receive phentermine. Then, based on our prior data, 60% of participants receiving phentermine monotherapy will NOT achieve ≥5% BMI reduction,[23] and will therefor go on to the second stage randomization. The hypothesized within-group standard deviation was based on our randomized trial of topiramate[24] and our observational data on phentermine use.[23] In these studies, the standard deviation of the percent change in BMI ranged from 3.5% to 6.3%. Table 2 indicates we have sufficient power to detect a 4% difference and even reasonable power across several scenarios to detect smaller changes.

Table 2. Aim 2 Power Calculation			
	Difference in BMI Percent Change		
Within Group SD	***3%***	***4%***	***5%***
3%	*99.0*	*99.9*	*100*
5%	*73.3*	*93.0*	*99.0*
7%	*45.3*	*69.0*	*86.7*

9.3 POPULATIONS FOR ANALYSES

There will be 2 analysis populations. Intent-to-treat (ITT) will include any participant randomized according to their treatment assignment. The safety population will include all who receive treatment, according to treatment received.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

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.

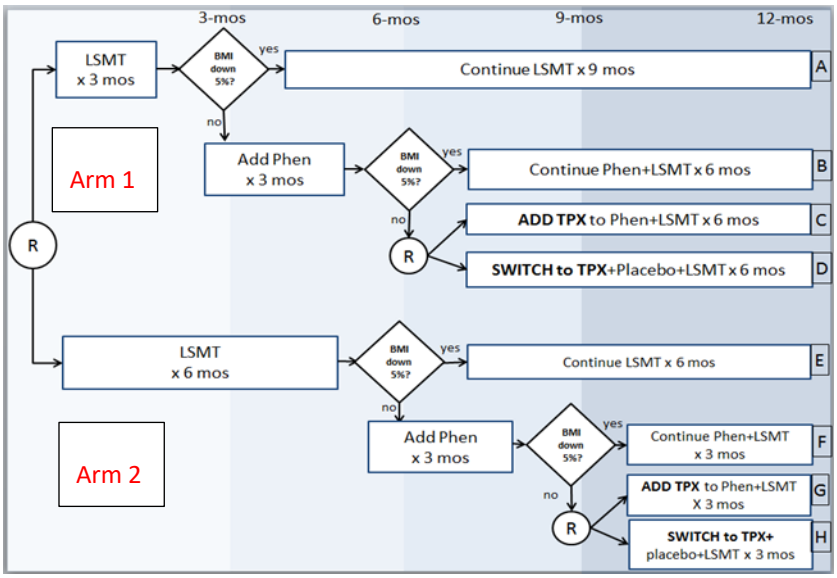
The proposed trial design of adaptive interventions is conceptually similar to a factorial design.[33,56-58] Similar to standard methods for factorial designs and adaptive intervention trials conducted in other therapeutic areas, analyses to address Aims 1 and 2 will be a test of the main effect of the randomized intervention. The primary (continuous) outcome for all analyses will be the percent change in BMI between baseline and 48 weeks. All efficacy analyses will be by intention-to-treat, and include all participants randomized to intervention, regardless of whether they are lost to follow-up. Statistical significance will be considered as $p<0.05$ for all analyses.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

To test the hypothesis specified for Aim 1, we will use a two-sample t-test to compare the mean percent change in BMI among those randomized to the 12-week assessment of LSMT (cells A+B+C+D in figure below) and those randomized to the 24-week assessment of LSMT (cells E+F+G+H). Secondary analyses will compare these groups using linear regression adjusting for important baseline characteristics such as age, sex, and BMI at baseline.

To test the hypothesis specified for Aim 2 which examines only the non-responders to LSMT+phentermine, we will use a two sample t-test to compare the mean percent change in BMI from second-stage randomization among those randomized to topiramate+phentermine (cells C+G) compared to those randomized to switch to topiramate monotherapy (cells D+H). Similar to Aim 1, secondary analyses will compare these groups using linear regression adjusting for important characteristics collected at baseline or at the time of second-stage randomization including percent change in BMI prior to randomization.

Importantly, although there may be small numbers of participants in any one particular cell (e.g., cell A) at the end of the trial, none of these analyses compare participants from a single cell to another single cell. Instead, as is common in factorial designs, we have pooled participants randomized to the same condition in order to test the main effects.



We will address missing response data using a variety of sensitivity analyses. Because the primary outcomes are collected longitudinally, we will fit a linear mixed effects model for the longitudinal trajectory of BMI and impute any missing 48 week BMI values from this longitudinal model for the primary analysis. This approach assumes that the outcomes are missing at random. We anticipate that non-response may depend on the unobserved BMI of the adolescent; that is, we assume a not missing at random (NMAR) missingness mechanism. Therefore, we will also consider joint longitudinal mixed-effects model of BMI and response status.[59] Following imputation, standard statistical methods can be applied

provided we properly account for the multiply imputed outcomes (using SAS Proc MIANALYZE).[60-62] We will also consider fitting pattern mixture and selection models which allow for NMAR missingness mechanism.[63] As a result of using these methods, all randomized subjects will be included in analyses, and over-recruitment for loss to follow-up will not be necessary.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints including 48-week change in body composition (percent body fat, visceral fat, lean body mass), cardiometabolic profile (blood pressure, fasting lipids, fasting glucose, hemoglobin A1c, ALT, AST) and quality of life will be compared between those randomized to 12-week and 24-week LSMT assessment, and between those LSMT+phentermine non-responders randomized to LSMT+topiramate+phentermine and LSMT+topiramate+placebo using similar analytical techniques as for the primary endpoint.

9.4.4 SAFETY ANALYSES

Safety analyses will use the safety population and will be primarily descriptive reporting the number and percentage of adverse events.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Anthropometrics – Height, weight, BMI, BMI percent of the 95th percentile
Demographics and environment – age, sex, race, ethnicity, family income, food insecurity, ACE Q Teen Social Support for Eating Habits, Social Support for Exercise
Blood pressure
Heart rate
Tanner stage
Labs – lipids, glucose, HbA1c, AST, ALT
Body composition - % body fat, visceral fat, lean body mass

Eating behaviors

- Questionnaire of Eating and Weight Patterns – Adolescent (binge eating behavior measure)
- Adult Eating Behavior Questionnaire
- Reward Based Eating Drive Scale X5 (hedonic eating)
- Dutch Eating Behavior Questionnaire (eating restraint, emotional eating, and external eating measure)

Neuropsychological function

- Behavior Rating Inventory of Executive Function – Self Report (BRIEF-SR) (executive function measure)
- NIH Tool Box (cognition battery)
- PROMIS Pediatric Short Form v 2.0 – Anxiety Symptoms 8a
- Impact of Weight on Quality of Life-Kids

9.4.6 PLANNED INTERIM ANALYSES

If 10% of participants have a serious adverse event after a minimum of 30% enrollment, the trial will be stopped.

9.4.7 SUB-GROUP ANALYSES

We will adjust analyses for age, sex, race/ethnicity but we will not have a sufficient sample size to do sub-analyses by these groupings.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

To test the effect of the proposed moderators (Aim 3), we will fit a linear regression model within the relevant subpopulation which includes a main effect for the randomized treatment group, the moderator, and moderator by treatment interactions. Wald-type tests will be used to assess if the interaction term is significant indicating that the covariate significantly moderates the proposed treatment effect. For example, to address if baseline binge eating moderates first-stage randomization, we will fit a linear regression model among all participants with covariates for first-stage randomization (12-week assessment of LSMT versus 24-week assessment of LSMT), indicator for binge eating, and their interaction. To evaluate if hunger is a moderator of second-stage randomization, we will fit a regression model among non-responders to LSMT+phentermine with covariates for second-line treatment (LSMT+topiramate+phentermine versus LSMT+topiramate+placebo), indicator for hunger, and their interaction.

To estimate the effect of potential mediators of pharmacotherapy (e.g., changes in resting energy expenditure), we will use standard regression-based estimators. Specifically, we will fit a linear regression model among non-responders to LSMT+phentermine for percent change in BMI including a term for the posited mediator (e.g., changes in resting energy expenditure), second-stage treatment (LSMT+topiramate+phentermine versus LSMT+topiramate+placebo), and other confounders of the mediator-outcome relationship and a model for change in the mediator with second-stage treatment and other covariates as predictors. The controlled direct effect can be estimated using the regression coefficient for second-line treatment in the adjusted outcome model and the indirect effect can be estimated as the product of the coefficient for second-line treatment in the mediator model and the coefficient of the mediator in the outcome model.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent and assent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol: parent consent, participant assent. A number of our potential participants have parent(s) whose primary language is Spanish. For that reason, a parental consent form will be made available in Spanish.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

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

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely

terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

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

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator.

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

The following types of research material will be obtained from the participants: blood specimens, anthropometric and other biometric data, reports of eating behavior, and neuropsychological testing information including symptoms of depression and anxiety. All material will be used exclusively for research. Pre-existing chart (electronic medical record) information may also be used. Data obtained will be stored in a confidential database without direct identifiers. The principal investigator and designated study staff will have access to the linkages, which will be stored in a separate, secured location. Hard copies of data, including source documents with identifiers, will be kept in locked file cabinets in a locked office until the completion and publication of the study, at which time any identifiers will be removed and data will be stored at a secure storage facility for 6 years. Access to the locked file cabinet will be given to the study coordinators and principal investigator only. Any study files that will be shared with the University of Minnesota will remove patient identifying information.

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

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the University of Minnesota. These samples could be used to research the causes of obesity, its complications and other conditions for which individuals with obesity are at increased risk, and to improve treatment.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Safety Director**
Claudia Fox, MD Associate Professor	Ania Jastreboff, MD, PhD Associate Professor
University of Minnesota	Yale University
2450 Riverside Ave, 6th floor east bldg.	1 Long Wharf Drive, New Haven, CT
612-626-6616	203-785-4081
Lusc0001@umn.edu	ania.jastreboff@yale.edu

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including a psychiatrist, a pediatric cardiologist, and a biostatistician. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet every six months to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the PI.

10.1.7 CLINICAL MONITORING

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

Monitoring will be done shortly after IRB approval (before subjects are enrolled) and then on an every six month basis. Consent and eligibility will be reviewed on 100% of subjects. Data will be reviewed on 10% of subjects. Study monitors will review the findings with the staff at the conclusion of the visit and the staff have 10 days to resolve as many of those findings as they can before the final report is generated. The monitoring report is generated on Day 11 after the visit.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report

form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap, a data capture system provided by the University of Minnesota. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the paper source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

All deviations must be addressed in study source documents, and reported to the NIDDK Program Official in the annual report. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the SOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

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

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

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 10 years after the completion of the primary endpoint by contacting the PI.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

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

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
DXA	Dual Energy X-ray Absorptiometry
EC	Ethics Committee

eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IWQOL-Kids	Impact of Weight on Quality of Life-Kids
LSMEANS	Least-squares Means
LSMT	Lifestyle Modification Therapy
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
Phen	Phentermine
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TPX	Topiramate
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

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

Version	Date	Description of Change	Brief Rationale
2.0	22 Jul 2019	• Provides information about the pediatric psychologist availability and the steps to be taken if a subject is identified as having suicidal ideation. • Revises the SAE reporting to the UM IRB to 5 days.	• Subject safety and detailed description of study procedures. • Matches protocol to current IRB policy.
3.0	24 Jul 2019	• Revises the dose titration for topiramate • Adds additional exclusion criteria • Adds information about who will conduct the Tanner staging • Discusses changes of decreases in bicarbonate and increases of creatinine in lab tests • Adds Depression and suicide screening to all in-person visits • Makes a revision to the Medical Safety Monitor, based on feedback from the NIH	• Changes made based on feedback from the U.S. Food and Drug Administration (FDA) • Changes made based on feedback from the NIH, NIDDK
4.0	18 Sep 2019	• Changes the timing of basic demographic collection from the baseline to screening. Lists each of the questionnaires to be performed, separates out the compliance check from the AE check, removes the SphygmoCor testing, and the optional biobanking was changed to a serial measurement • Removed the Dutch Eating Behavior Questionnaire and replaced it with the Adult Eating Behavior Questionnaire	

		• Removed the POWER of Food Scale and replaced it with the Reward-Based Eating Drive Scale X5 • Added Impact of Weight on Quality of Life-Kids to the list of assessments • Removed the SphygmoCor testing due to funding limitations and because the test has little clinical applicability to measuring the safety of the medications being used in this study • The meal test was changed from 4 hours to 2 hours and the gastric emptying study was removed due to funding limitations	
5.0	01Oct2019	Provides consistency regarding when for blood pressure/heart rate will be collected, the frequency of iDXA scans, and the frequency of adverse event reviews	Corrects small discrepancies between the schedule of events and the protocol activities
6.0	14Nov2019	Removes a specific brand of protein drink to be used for the meal test, and clarifies when adverse events will be assessed due to a discrepancy in the protocol	Allows flexibility for the use of protein drinks since some brands have not been readily available. Also corrects discrepancies between the schedule of events and the listed protocol activities with regard to when adverse events will be assessed.
7.0	11Dec2019	Removes the CPT and PROMIS Depression tests from the project	The CPT is being removed due to the time intensive nature that it takes the subjects to fill out. The PROMIS Depression is being removed as depression is already being assessed by the PHQ9.
8.0	10Jan2020	Changes the adverse event relatedness terms to be more in line with wording that is typically utilized. Notes that AEs are to be captured at every subject visit. The PI will review	Protocol clarifications

		them regularly but not within 24 hours of a visit	
9.0	11Mar2020	Clarifies the exclusion criteria. Individuals who are on an SSRI must be on a stable dose for at least 3 months.	Exclusion clarification
10.00	18Jun2020	Clarifies that the reporting of deviations will be done according to CPOM Standard Operating Procedures (SOPs)	Clarification. CPOM utilizes SOPs and not MOPs.
11.0	20Jul2020	Removes the meal test from Week 12, Week 24, Week 36 and Week 48 Clarifies that non-serious AEs can be reported to reviewing entities upon request	Budgetary constraints The UM IRB and the FDA do not require that non-serious AEs be reported annually, but this information is always available.
12.0	15Sep2020	Notes that a Spanish language parental consent form has been created in order to enroll participants whose parent(s) primary language is Spanish	Translating the parental consent into Spanish form will help to provide opportunities for a broader population.
13.0	21Oct2020	Removes the indirect calorimetry testing	Removed from the project due to concerns with being able to thoroughly clean the equipment during the COVID-19 pandemic.
14.0	19Mar2021	Revises the exclusion criteria surrounding depression and suicidality. The blood pressure exclusion has been modified to be stratified based on age. Adds in questions about satisfaction with weight loss goals and medication assignment.	Revisions to the exclusions surrounding depression and suicidality are based on FDA suggestions. The blood pressure exclusion is a clarification. The questions will allow us to help determine if participants were happy with their treatment assignment and how they felt about the medications they were assigned to take.
15.0	14Dec2021	Will ask participants to bring their study medication with them to all in-person visits for compliance. Individuals who do not bring their medication will be asked about compliance. Participants will now be asked about their dietary choices and activities. Updates the location of the freezer.	We are making revisions to how we gather information about study medication compliance and gathering information on dietary choices and activity levels.

16.0	11Feb2022	We will be collecting information on adverse events and concomitant medications at the Week 72 visit.	We are collecting adverse event information for safety. We are asking about concomitant medications at the Week 72 visit to help assess how long participants were able to maintain their weight loss after stopping the study medication or whether they started a weight altering medication as part of their clinical care after they were done taking the study medication.
17.0	27Jun2022	Clarifies who can conduct Tanner staging.	Tanner staging may be conducted by an individual who has adequate documentation of training as long as it is within their licensure requirements.
18.0	31Aug2022	Adds in recruitment via use of the MyChart messaging in EPIC	To increase enrollment.
19.0	09May2024	Corrects the Schedule of Activities table (section 1.2) to correct an error associated with MOD13409 and when compliance checks might be done for individuals who are placed on medication	Corrects a typographical error
20.0	01Jul2024	Revises section 8.2 of the protocol with regard to the PHQ-9 and C-SSRS tests.	Expands staff actions for review of the PHQ-9 and C-SSRS tests for subject safety.

11 REFERENCES

Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE). Include citations to product information such as manufacturer's IB, package insert, and device labeling.

Examples:

- ***Journal citation***
  Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. J Natl Cancer Inst. 2007 Feb 21;99(4):258-60.
- ***Whole book citation***
  Belitz HD, Grosch W, Schieberle P. Food chemistry. 3rd rev. ed. Burghagen MM, translator. Berlin: Springer; 2004. 1070 p.
- ***Chapter in a book citation***
  Riffenburgh RH. Statistics in medicine. 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; c2006. Chapter 24, Regression and correlation methods; p. 447-86.
- ***Web Site citation***
  Complementary/Integrative Medicine [Internet]. Houston: University of Texas, M.D. Anderson Cancer Center; c2007 [cited 2007 Feb 21]. Available from: http://www.manderson.org/departments/CIMER/.
- ***Electronic Mail citation***
  Backus, Joyce. Physician Internet search behavior: detailed study [Internet]. Message to: Karen Patrias. 2007 Mar 27 [cited 2007 Mar 28]. [2 paragraphs]
- ***References to package insert, device labeling or investigational brochure***
  Cite date accessed, version number, and source of product information.

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