Official Title: Phentermine/Topiramate in Adolescents with Type 2 Diabetes and Obesity

NCT#: NCT04881799

Date of the Protocol: 2024Dec10

ANCILLARY REVIEWS

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
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☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
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Protocol Title	Phentermine/topiramate in Adolescents with Type 2 Diabetes and Obesity
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Scientific Assessment	Nationally-based, federal funding organizations
IND/IDE # (if applicable)	158959
IND/IDE Holder	Megan Bensignor, MD
Investigational Drug Services # (if applicable)	5826
Version Number/Date:	Version 17.0, Dated 10Dec2024

PROTOCOL COVER PAGE

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	2.0	Change in the medication to be used in this study and update to the known risks of the new study medication. Health-related Pediatric-Quality of Life measures will also be added at baseline, 6 and 12 months.	Yes
2	3.0	Changes dictated by FDA letter; addition of lifestyle modification; assessment of TSH at baseline and lipid profile, basic metabolic panel and vitamin D at baseline, 6 and 12 months; PHQ-9 modified for teens will be used for participants from 12 to <18; addition of several exclusion criteria per FDA recommendations	Yes
3	4.0	• Adds a $20 payment at Week 20 for the upload of CGM data. • Revises the visits at Week 12 and 36 to be conducted in person with addition of anthropometrics, vital signs, and A1c to be done at CRU. • Removes screening labs. • Collects weight measurements monthly. • Updates the schedule of events to note when additional CGM sensors will be dispensed • Allows flexibility of in-person monthly visits after week 24 visit • Added instructions of CGM upload, water bottle and bags to patient facing materials	Yes

4	5.0	Modifies section 9 of the protocol to indicate that the study will secure consent from parents who are non-English speakers and submits a Spanish language parental consent form.	Yes, creates a Spanish language parental consent form
5	6.0	Modifies section 10.2 to note that endocrinologists at Park Nicollet and Children's may provide flyers to their patients who appear to qualify for the study. Revises the exclusion criteria for medications that we anticipate may become FDA-approved for pediatrics during the course of the project.	Yes, to make clarifications to the scales.
6	7.0	Modification of exclusion criteria to now include those treated with liraglutide at its 1.8 mg dose and exenatide ER.	Yes
7	8.0	Splits the screening visit into two parts: a screening and a baseline visit with the addition of $75 in compensation for the screening visit. Modifies recruitment to allow Dr. Bensignor to directly reach out to primary care providers or primary endocrinologists of eligible patients identified through BPIC data pull. Corrects the numbering of the references for the study.	Yes
8	9.0	Corrects discrepancies between the schedule of events and description of study activities	Yes
9	10.0	Updates the IND holder on the cover page of the protocol, revises section 4.2 of the protocol which discusses how IDS holds the randomization key and can break the blind for a participant if an emergency arises, and how they will destroy the medication returned by subjects.	No

10	11.0	Clarifies section 4.2 of the protocol with regard to medication dispensing for the open label portion of the study. Revises section 10.1 to add that the study coordinator may initiate telephone contact after recruitment letters are sent.	
11	12.0	Revises sections 10.1 and 10.3 to note that Children's of Minnesota will send out recruitment letters	No
12	13.0	Revises the protocol to note that the Dexcom G7 will be phased in as the CGM to be used for the study. The Dexcom G7 does not require swiping so compensation plan has been reworded.	Yes
13	14.0	Revises the exclusion criteria to allow individuals with febrile seizures to enroll in the study	No
14	15.0	Corrects the schedule of events and protocol language to be consistent with the study consent forms. Revises the parental consent and adult consent forms to note that study medication should be returned at Weeks 12, 24, 36 and 52 for compliance. Adds into the assent form the risks of physical exams and Tanner staging.	Yes
15	16.0	Revises the study so that if a participant arrives without having withheld insulin for the hours required for the OGTT testing ,the visit will proceed without the OGTT but the participant will be asked to return within one week to complete the OGTT testing.	No
16	17.0	Modifies section 4.1 of the protocol to note when participants will be taken off of basal insulin. Updates the risks section to note that kidney stones are a known risk of topiramate, one of the components of Qsymia.	Yes

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ABBREVIATIONS/DEFINITIONS

A1c	Glycated hemoglobin
AE	Adverse event
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
CCRC	Certified Clinical Research Coordinator
CFR	U.S. Code of Federal Regulations
CGM	Continuous glucose monitor
CI	Confidence interval
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CTSI	Clinical and Translational Science Institute
DPP-IVi	Dipeptidyl peptidase-4 inhibitors
DSMB	Data and Safety Monitoring Board
EDE-Q	Eating Disorder Examination Questionnaire
EKG	Electrocardiogram
FDA	U.S. Food and Drug Administration
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c, glycated hemoglobin
HIPAA	Health Information Portability and Accountability Act
HR	Heart rate
ICH GCP	International Code of Harmonisation-Good Clinical Practice
ICS	Informatics consulting service
IDS	Investigational drug service
iDXA	Dual energy x-ray absorptiometry
IE	Information exchange
ITT	Intent-to-Treat
IRB	Institutional Review Board
MCMC	Markov Chain Monte Carlo
MEN-1	Multiple Endocrine Neoplasia-1
oDI	Oral deposition index
OGTT	Oral glucose tolerance test
PHN/TPM	Phentermine/Topiramate
PHQ-9	Patient Health Questionnaire
PI	Principal investigator
PP	Per-protocol
QoL	Quality of life
RISE Study	Restoring Insulin Secretion Pediatric Medication Study
SAE	Serious adverse event
T2D	Type 2 diabetes
Teen LABS	Teen-Longitudinal Assessment of Bariatric Surgery Study
TODAY Study	Treatment Options for T2DM for Adolescents and Youth Study
U.S.	United States

1.0 Objectives

1.1 Purpose:

We will conduct a pilot, pragmatic, randomized trial with a 6-month placebo-controlled period followed by a 6-month open-label extension, investigating the effects of phentermine/topiramate (PHN/TPM) on BMI, insulin sensitivity, and glycemic control compared to placebo plus standard treatment (metformin +insulin) in adolescents with T2D. The purpose of this study is to 1) evaluate the effects of PHN/TPM vs. placebo+ standard treatment on BMI in adolescents with T2D and obesity and 2) evaluate the effects of PHN/TPM vs. placebo + standard treatment on insulin sensitivity and B-cell function in adolescents with T2D and obesity.

2.0 Background

2.1 Significance of Research Question/Purpose:

As the prevalence of obesity rises in the U.S., so does the incidence of pediatric type 2 diabetes (T2D), which is associated with more aggressive disease progression than in adults. From 2002-2012, the incidence of T2D in youth increased by 7% annually in the U.S.[1] Compared to adults, T2D in adolescents is a much more progressive and recalcitrant disease, characterized by more rapid deterioration of β-cell function and earlier incidence of exogenous insulin dependence and diabetes-related comorbidities.[2] A potential factor that drives the rapid progression of adolescent T2D is obesity (body mass index [BMI] >95th percentile.[3,4] Lifestyle interventions focused on weight reduction is an essential part of initial and long-term treatment for pediatric T2D. A body mass index (BMI) reduction of about 8% has been found to decrease insulin resistance in adolescents with T2D.[5] A 7-10% decrease in excess weight is also recommended by the ADA for pediatric T2DM.[38] However, current treatment guidelines for T2D recommend lifestyle management and metformin as first-line therapy, which rarely achieve such a BMI reduction in adolescents.[6, 7, 8]

There are limited medical therapies that effectively and concurrently improve glycemic control, reduce obesity, and beneficially impact β-cell function and insulin sensitivity in adolescents with T2D. Current treatment guidelines for pediatric T2D recommend lifestyle management and metformin as first-line therapies,[6-8] which rarely achieve meaningful BMI reduction in adolescents.[2, 9-13] The Treatment Options for T2DM for Adolescents and Youth (TODAY) study showed that metformin monotherapy and metformin plus lifestyle management were less effective in adolescents than adults, resulting in increased BMI and visceral body fat.[2,13-14] About half of participants (52%) on metformin

monotherapy and 47% on metformin and intensive lifestyle therapies progressed to exogenous insulin dependence within four years.[2] Furthermore, the Restoring Insulin Secretion (RISE) Pediatric Medication Study demonstrated that metformin + insulin did not slow the progression of β-cell deterioration in adolescents with T2D or impaired glucose tolerance.[12] Making matters worse, insulin-associated weight gain can increase BMI and body fat, and exacerbate insulin resistance, requiring the use of additional insulin therapy.[15]Conversely, tight glycemic control is imperative as adolescents with T2D are also more likely to have diabetes-related comorbidities such as hypertension, atherosclerosis, and kidney disease (albuminuria) earlier compared to adults.[2]

Even the two-newly FDA-approved glucagon-like peptide receptor agonists (GLP-1RAs) for youth ≥ 10 years with T2DM (liraglutide 1.8 mg and exenatide ER) did not result in the weight reduction recommended for pediatric patients by the ADA.[39-41] For example, liraglutide at doses up to 1.8 mg/day did not significantly reduce BMI in 134 adolescents, aged 10-17 years with T2DM and overweight/obesity (mean BMI of 33.90 + 9.25 kg/m2) after a 26-week double-blind randomized, control trial (RCT).[40] At the end of the 26-week open-label extension of this trial, a minimal estimated treatment difference in BMI of -0.89 kg/m2 or a 2.73% decrease between liraglutide and placebo groups was found.[39,40] Although the BMI reduction with liraglutide 1.8mg/day is statistically significant, it remains unclear the clinical significance of this finding. Exenatide ER also did not significantly reduce weight compared to placebo after a 24-week randomized controlled trial (-0.59 + 0.665 kg vs + 0.63 + 0.882. kg, respectively, p=0.307) and the 28 open-label extension (0.04+ 6.09 kg versus -0.04 + 4.69 kg, respectively) of 84 In the randomized control trial of adolescents with obesity (mean BMI: 36.36 +8.57 kg/m2) and T2DM, previously treated with diet and exercise alone or with metformin + a sulfonylurea and/or insulin.[41]

Only bariatric surgery has been shown to be a long-term effective treatment for T2D, improving both BMI and glycemic control (A1c), more significantly than insulin and metformin therapy in adolescents.[16-17]A secondary analysis comparing adolescents with T2D treated with bariatric surgery (Teen-Longitudinal Assessment of Bariatric Surgery [LABS] Study) and adolescents with T2D treated with medication (TODAY Study) found that mean A1c decreased from 6.8% to 5.5% in adolescents who underwent bariatric surgery compared to a mean A1c increase from 6.4% to 7.8% in TODAY participants.[16] Additionally, the mean BMI in the Teen-LABS cohort decreased by 29.0% from baseline compared with a 3.7% increase in TODAY participants during the 2-year follow-up.[16] However, bariatric surgery is not a feasible therapy for all patients. Scalable, non-surgical strategies for the management of T2D in adolescence which lead to meaningful clinical BMI reduction and decrease in insulin resistance are needed.

A combination of two oral anti-obesity pharmacotherapies, phentermine and topiramate (PHN/TPM), is now FDA-approved to treat obesity in the pediatric population for patients ≥ 12 years of age with obesity. About 31% of adolescent participants without diabetes with a BMI of 37.8 ± 7.1 kg/^{2} receiving mid-dose PHN/TPM and 42.5 % receiving top dose compared to 0% receiving placebo achieved at least a 10% weight reduction over 1 year in a recent randomized control trial. In this trial, triglycerides significantly decreased by 12% with both mid-dose and top-dose compared to an 8% increase with placebo. This finding is of particular interest as excess circulating triglycerides accumulate in muscle, liver, and pancreatic cells, leading to insulin resistance and β-cell dysfunction during the pathogenesis of T2DM. Although, weight reduction can decrease intra-pancreatic lipid content, normalize pancreatic morphology, and restore first-phase insulin secretion in adults with T2DM, it is not known if reduction in serum triglycerides will improve β-cell function, particularly in youth with rapidly progressing diabetes.

The rationale for specifically focusing on PHN/TPM (vs. other medications, including GLP-1RAs) to reduce BMI is supported by feasibility of attainment of study drug for a pilot study as well as ease of administration as it is a daily oral medication. PHN/TPM also have multiple mechanisms of action, which are thought to target many of the counter-regulatory biological adaptation, which prevent weight loss. These mechanisms include: 1) reducing appetite through inhibition of norepinephrine reuptake (phentermine) and reduction of hypothalamic glutamate neurotransmission (topiramate) and lowering the levels of neuropeptide Y (topiramate); 2) enhancing satiety by slowing gastric emptying (combination of PHN/TPM); and 3) increasing energy expenditure (both phentermine and topiramate independently).[24-30] While other obesity medications target some of these pathways, their respective mechanisms of action are generally less comprehensive, and accordingly have lower efficacy, ranging from 3-5% placebo-subtracted weight reduction at 1 year, or are injectable medications, which may decrease treatment adherence.[31] PHN/TPM offers the potential to achieve greater BMI reduction than standard diabetes treatment of metformin ± insulin.

2.2 Existing Literature:

To our knowledge, no PHN/TPM trials have been conducted in adolescents with T2D with a primary focus on BMI reduction, and improvement in β-cell function. Therefore, our focus will be novel for the field of pediatric T2D research. Based on adult outcomes with PHN/TPM, we anticipate a mean placebo-subtracted BMI reduction of 8-10% at 52 weeks, a level considered clinically-meaningful in adolescents and will help improve insulin resistance.[5, 19, 31-33]

Treatment Effect of Phentermine/Topiramate in Adults

Phentermine/topiramate was approved by the FDA in 2012 for the treatment of obesity in adults. This orally-administered medication is available in mid- (phentermine 7.5 mg; topiramate 46 mg) and high- (phentermine 15 mg; topiramate 92 mg) doses, administered once per day. In a meta-analysis, phentermine/topiramate was shown to be one of the most effective obesity medications currently available.[34] A large dose-ranging trial in adults evaluating phentermine and topiramate as monotherapies vs. phentermine/topiramate demonstrated superior efficacy of the combination with an acceptable safety profile.[35]

Results from a large phase III clinical trial demonstrated placebo-subtracted weight loss of >9% with treatment for one year at the top dose.[36] Importantly, a separate trial demonstrated that the treatment effect is durable out to at least two years.[437]The most common side effects in these trials were paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth. Improvements were noted in blood pressure, lipids, glucose, insulin, HOMA-IR, C-reactive protein, and adiponectin.

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

We performed a chart review of patients treated with phentermine and topiramate within our pediatric weight management clinic. Our healthcare providers carefully and systematically assess and document adverse events with obesity pharmacotherapy at all follow-up visits according to established protocols. We identified 55 patients (37 females/18 males) ages 11-20 years old (mean age 15.4±2.3 years) with a baseline mean BMI of 43.2±10.2 kg/m2. The most commonly prescribed doses were 15 mg/day of phentermine and 75-100 mg/day of topiramate. The mean duration of combination treatment was 11.1±10.3 months. Owing to variability regarding how these medications were prescribed in the clinic, we do not report on changes in BMI. In other words, many patients were started on either phentermine or topiramate monotherapy followed by the addition of the other medication at a later time-point. Table 1 summarizes: 1) the incidence of the most commonly reported adverse events; 2) the percent of patients experiencing resolution of the adverse event(s) while remaining on treatment; and 3) the percent of patients that discontinued treatment as a result of the adverse event(s). Overall, results demonstrated a low incidence of adverse events with a relatively high rate of resolution. Importantly, only a small percentage of the patients discontinued therapy as a result of adverse events. Therefore, these results provide preliminary evidence supporting

the safety of these medications and demonstrate a reasonably high level of acceptability and tolerability in the adolescent population.

Table 1. Adverse Events, Resolution, and Acceptability of Phentermine/ Topiramate Treatment

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

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

The manufacturer of phentermine/topiramate recently completed a pharmacokinetic trial among adolescents (12-17 years old) with obesity (BMI ≥95th percentile) and shared the results with our group. Here we report on participants that were randomized to either placebo (N=14; 9 females) or high-dose phentermine/topiramate (15 mg/92 mg) (N=13; 9 females) and received treatment for 56-days. In brief, pharmacokinetic results were similar to adults. In aggregate, adverse events were experienced by 50% of the placebo group and 77% of the phentermine/topiramate group. Details of the adverse events are shown in Table 2.

Table 2. Adverse Events of Phentermine/Topiramate Treatment in Adolescents with Obesity

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

At 56 days, the percent change in body weight was +1.1±2.8% in the placebo group and -5.0±3.4% in the PHN/TPM group (placebo-subtracted weight loss of 6.1%). Owing to the relatively small sample size and the fact that weight reduction was a secondary outcome variable, the manufacturer did not perform a statistical analysis on these results. However, the preliminary results further support our estimated treatment effect, particularly considering the treatment period was only two months (56 days). Indeed, the degree of placebo-subtracted

weight loss was slightly better than what was observed in the adult trials at the two-month time-point, suggesting that the effects are at least additive when these two medications are used together.

In summary, this portfolio of preliminary work: 1) demonstrates our Center's leadership role in, and commitment to, the field of pediatric obesity medicine; 2) highlights the benefits (weight loss and cardiometabolic risk factor improvement) as well as our experience with this intervention; 3) provides preliminary evidence supporting the safety, efficacy, and acceptability of combination therapy in adolescents with severe obesity; and 4) sets the stage for taking this next important step.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

- To evaluate the effects of PHN/TPM vs. placebo + standard treatment (metformin ± insulin ± liraglutide 1.8 mg or exenatide ER) on BMI in adolescents with T2D and obesity.

3.2 Secondary Endpoints/Events/Outcomes:

- To evaluate the effects of PHN/TPM vs. placebo + standard treatment on insulin sensitivity and β-cell function in adolescents with T2D and obesity.

3.3 Exploratory Endpoints/Events/Outcomes

- To evaluate the effects of PHN/TPM on total and visceral body fat
- To evaluate the effects of PHN/TPM vs. placebo + standard treatment on cardiometabolic measures (lipid panel [TC, LDL-C, TG, HDL-C], blood pressure and heart rate).

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

4.1 Description:

Phentermine/topiramate Therapy

Participants randomized to PHN/TPM will initiate treatment at 3.75 mg/23 mg orally once daily in the morning for 14 days, which will then be increased to 7.5 mg/46 mg orally once daily in the morning for 14 days, which will then be increased to 11.25 mg/69 mg orally once daily in the morning for 14 days, which will then be increased to 15 mg/92 mg orally once daily in the morning for the remainder of the trial. There will not be a pause in dose titration between weeks 4 and 12 as indicated by the medication labeling as this pause is indicated to clinically assess weight loss response on mid-dose PHN/TPM before up-titrating to high-dose PHN/TPM. However, the goal of this proposed study is to assess BMI reduction on the maximum tolerated dose of PHN/TPM in a clinical research setting. Therefore, an assessment of weight loss on the moderate dose of

PHN/TPM between weeks 4 and 12 is not warranted. Participants unable to tolerate the dosing regimen will be maintained at the maximally tolerated dose. Following the final study visit, all participants will be down-titrated gradually by taking medication every other day for seven days before stopping treatment altogether. PHN/TPM will be purchased from an independent vendor by the University of Minnesota Investigational Drug Service Pharmacy (IDS). Placebo will be manufactured by IDS. The placebo capsules manufactured by IDS will not be able to be matched to the commercial product. The PI and research coordinator will not be involved in pill counting to evaluate adherence for this trial in order to preserve the blinding of investigators. Participants will not be told which treatment arm they are in to preserve the blinding of participants. Participants will be instructed to take the medication under the supervision of a parent/guardian and pill counts of returned product will serve as a proxy of treatment adherence. If the average fasting plasma glucose (FPG), measured by CGM, is >185 mg/dL after titration to PHN/TPM 15mg/92mg or maximum tolerated dose, metformin therapy or basal insulin therapy will be started or titrated for a goal average FPG <110 mg/dL.

Metformin Therapy

Participants who are on metformin therapy prior to enrollment will remain on metformin, if tolerated. Titration and maximum tolerated dose will be at the discretion of the principal investigator and a dose of 2000 mg daily will be targeted if CGM is > 185 mg/dL after titration to PHN/TPM 15mg/92or maximum tolerated dose.

Insulin Therapy

Insulin will be started per the American Diabetes Association guidelines on any participants whose A1c is >8.5%. For those treated with insulin prior to enrollment, basal insulin dose will be reduced by 20% at start of PHN/TPM therapy and then by 20% every 4 weeks if average FPG is <110 ml/dL. Basal insulin dose will continue to be reduced every four weeks until basal insulin dose is below 0.2 units/kg/day and then basal insulin will be stopped. If the FPG value is >185 mg/dL after titration to maximum tolerated dose of PHN/TPM and metformin, basal insulin therapy will be started or titrated up by 20% until for a goal average FPG <110 mg/dL. If participants are on rapid-acting insulin meal dosing (carbohydrate coverage), this will be discontinued at the start of the PHN/TPM therapy and only restarted if two-hour post-prandial plasma glucose >200 md/dL. Rapid-acting insulin will be used as a rescue medication for BG >200 mg/dL per PI discretion.

4.2 Drug/Device Handling:

The PHN/TPM that will be used for this study will be stored with the IDS pharmacy. Placebo will be manufactured by IDS. The IDS pharmacy specializes in storing and dispensing investigational drugs for clinical trials. Study physicians will write a prescription in order for IDS to dispense the study medication. IDS is a secure facility (behind two locked doors) and maintains refrigerators and freezers with temperature tracking to assure that the drugs utilized in this study will maintain stability. IDS will keep detailed records on the receipt of investigational product (including lot numbers) and detailed records on the dispensing of product to each subject enrolled in the study. IDS is also equipped to destroy any medication that remains at the end of the study or any product that is returned by the study participants. IDS will also be hold the randomization key for the study, which was developed by the study biostatistician, and will follow their internal standard operating procedures for breaking the blind in the event of an emergency.

When an individual participant transitions from the placebo-controlled portion of the study to the open-label portion of the study, the study physician will put in orders for the open label study for IDS to dispense medication and the IDS staff will review the patient randomization and will either continue to fill the prescription with the maintenance dose or fill the prescription to have the participant titrate up on the study medication in order to help keep the study team blinded.

4.3 Biosafety:
Not applicable.

4.4 Stem Cells:
Not applicable.

4.5 Fetal Tissue:
Not applicable

5.0 Procedures Involved

5.1 Study Design:

This is a pilot, pragmatic, randomized trial with 6-month placebo-controlled period followed by a 6-month open label extension. Thirty pubertal or post-pubertal adolescents will be randomized into one of two arms:

- PHN/TPM
- Placebo

Participants will engage in typical T2D clinical care and lifestyle management, with the addition of PHN/TPM or placebo therapy for 6 months followed by a 6-month open label extension during which all participants will be given PHN/TPM in an unblinded fashion.

The schedule of events (below) shows the data that will be collected at each study visit.

Schedule of Events

	Screening	Baseline	Placebo-Controlled												
Week	-4%	0%	4	8	12%	16	20	24%	28	32	36%	40	44	48	52%
Informed consent/assent	X														
Demographics	X														
Medical and medication history	X														
Review of inclusion/exclusion criteria	X														
Randomization		X													
Urine pregnancy test[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X			X			X			X				X
Tanner staging	X				X			X			X				X
Anthropometrics[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (Blood pressure and heart rate)	X	X			X			X			X				X
EKG		X													
Contraceptive counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X
Hemoglobin A1c		X			X			X			X				X
Eating Disorder Examination Questionnaire (EDE-Q)		X			X			X			X				X
Peds-QOL (general and diabetes modules)		X						X							X
Patient Health Questionnaire (PHQ-9)	X				X			X			X				X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X				X			X			X				X
Total daily insulin dose assessment		X			X			X			X				X
Oral Glucose Tolerance Test (OGTT)		X						X							X
ALT, AST, INR, TSH, bilirubin, albumin, basic metabolic panel	X							X							X
Lipid profile, vitamin D 1,25[b]		X													
Plasma glucose level[b]		X						X							X
c-peptide level[b]		X						X							X
Insulin level[b]		X						X							X
iDXA (visceral and total body fat and bone mineral density)		X						X							X
Review of CGM data[c]			X	X	X	X	X	X	X	X	X	X	X	X	X
Insulin titration per CGM			X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense new CGM sensor			X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study medication		X	X	X	X	X	X	X	X	X	X	X	X	X	
Review of medication adherence					X			X			X				X
Review of co-administered drugs	X	X			X			X			X				X
Lifestyle and behavior counseling		X			X			X			X				X

Highlighted "X" will be done in the Clinical Research Unit. Non-highlighted X will be done in the Delaware Clinical Research Center

a Including height and weight at Weeks 0, 12, 24, 36 and 52. Weight only will be done at Weeks 4, 8, 16, 20, 28, 32, 40, 44, 48. Weight done remotely via Bluetooth monthly if there are no in-person visit scheduled for weeks28, 32, 40, 44, and 48.

b Blood will be drawn during the OGTT at baseline, 30-, 60-, 90- and 120-minutes following glucose ingestion

c Continuous glucose monitoring with CGM data will be reviewed with participant via telephone after upload by PI or Marrissa Ludwig, Clinical Diabetes Educator.

d Urine pregnancy tests will be done on all females of childbearing potential. Tests will be done at in-person or at home.

$ Visit windows for Weeks 4-52 are +/-7 days from the baseline visit

% In-person visits

5.2 Study Procedures:

Physical exam: A study physician will conduct a physical examination to ensure the participant is healthy enough to enroll in the study. A pubertal status will also be undertaken by the study physician (Dr. Bensignor) who is a trained pediatric endocrinologist. She has been trained in the proper technique to assess pubertal stages and will be the same study physician conducting all assessments throughout the trial.

Vital signs: Blood pressure (BP) and heart rate (HR) will be collected.

Hemoglobin A1c: Blood will be collected for a hemoglobin A1c level.

EKG: Electrocardiogram will be performed at screening/baseline visit and per PI discretion.

Eating Disorder Examination Questionnaire (EDE-Q): The EDE-Q identifies disordered eating behaviors and unhealthy attitudes about weight, such as purging, unhealthy obsession with dieting and/or body weight, prolonged fasting/starvation, use of laxatives to control weight and excessive exercise.

Patient Health Questionnaire-9 (PHQ-9): The PHQ-9 measures depression and suicidality. The PHQ-9 Modified for Teens will be administered to participants < 18 years of age. A participant will be referred to a mental health professional or primary care provider if s/he has a PHQ-9 score of $\geq$ 10 or reports any suicidal behavior. A PHQ-9 score $\geq$ 15 at the screening vision is an exclusion criteria.

Columbia-Suicide Severity Rating Scale (C-SSRS): The C-SSRS measures depression and suicidality. A participant will be referred to a mental health professional or primary care provider if s/he has any suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS. Please see Exclusion Criteria for cut-off scores related to the C-SSRS.

Pediatric Quality of Life Inventory (PedsQL^{TM}): The PedsQL measures general and disease-specific quality of life. We will be using the participant-reported measures for the PedsQL^{TM} Generic Core Scales and Diabetes Module Version 3.2 for young adults (aged 18-25 years) and Teens (12-18 years).

Oral Glucose Tolerance Test (OGTT): Insulin sensitivity and β-cell function will be measured via a 2-hour, 75 mg oral glucose tolerance test. OGTT has been widely used in the evaluation of β-cell dysfunction and T2D, including in the TODAY and RISE studies.[2,12] The OGTT will be performed following a 10-12 hour overnight fast. Participants will take their last dose of metformin (if applicable) the evening before testing. Participants on basal or bolus insulin will be asked to withhold insulin dose either 36 hours or 6 hours, respectively, prior to testing. Plasma glucose levels, C-peptide, and insulin levels will be measured at baseline, 30, 60, 90 and 120 minutes following standard glucose ingestion. If a participant comes to a visit and has not withheld insulin for the required number of hours, the visit

will proceed without the OGTT and the participant will be asked to return to perform the OGTT within one week of the originally scheduled visit.

Glycemic Control: Time in range (BG of 70-180 mg/dL) and hypoglycemic events will be measured using Continuous Glucose Monitors, either Freestyle Libre 14 day or Dexcom G7. The Freestyle Libre 14 day is no longer being produced so we will phase in the use of Dexcom G7 CGM. Worn on the skin, the disposable, single use sensor will continually measure glucose levels from the interstitium, every minute for 14 days (Libre) or 10 days (Dexcom G7) and will upload the data for review, and the participant will be asked to share this data with the study team. Participants will be taught how to place and replace the CGM. Participants who have a Libre CGM will be instructed to swipe the sensor at least twice daily (fasting and at bedtime) and to upload their CGM data monthly. Participants who have the Dexcom CGM will not need to swipe, but will be instructed to upload their CGM data monthly. CGM data will also be used to titrate insulin and metformin dosing. Percent time of CGM use will be used to assess adherence.

Total daily insulin dose: For participants on insulin therapy, total daily insulin dose (units/kg/day) will be averaged over the previous month at each study visits. Participants will log their insulin doses and return pens to study visits.

Body composition: Total body and visceral fat (% and kg) and measures of bone mineral density will be measured by dual energy x-ray absorptiometry (iDXA). iDXA measurements, using standard positioning techniques, will be conducted and analyzed by trained staff.

Anthropometrics: Height and weight will be collected by trained research staff at weeks 0, 12, 24, 36 and 52. Weight only will be collected at Weeks 4, 8, 16, 20, 28, 32, 40, 44, and 48. Weight will be collected via a scale provided to the participants and reported directly to the research coordinator at Week 28, 32, 40, 44, and 48 if there no monthly visits and per the PI's discretion.

Lifestyle and behavior management: All participants, regardless of drug/placebo assignment, will receive the same lifestyle/behavioral modification counseling monthly throughout the entire study: delivered at each in-person and virtual study visit (screening/baseline visit prior to randomization and weeks 12, 24, 36, and 52). The lifestyle/behavioral modification curriculum has been adapted from the NIDDK-sponsored TODAY study lifestyle modification program materials and is based on principles detailed in U.S. Preventive Services Task Force screening recommendation statement and utilized by our group in a previous and ongoing trials. Trained study coordinators will deliver the lifestyle/behavioral modification counseling, which will focus on small, successive changes in dietary physical activity behaviors through the use of evidence-based behavior change strategies such as self-monitoring, goal setting, reinforcement for goal achievement, stimulus control, social support, problem solving, and motivational techniques.

This will include guidance on a hypocaloric diet (500 calorie per day deficit) and increasing physical activity.

5.3 Study Duration:
This pilot study will enroll approximately 30 participants. Participation will last for approximately 52 weeks.

We anticipate that it will take 36 months to enroll and have all 30 participants complete 52 weeks of treatment.

5.4 Use of Radiation*:*

The iDXA used in this study uses radiation to generate its picture. The average iDXA is equal to a few hours of ionizing radiation exposure in Minnesota. The AURPAC will be asked to review the consent form language and dosimetry calculations to ensure that they are correct.

6.0 Data and Specimen Banking: Not applicable

7.0 Sharing of Results with Participants

7.1 The results of tests done during the study will be shared with participants upon request.

7.2 Sharing of genetic testing: Not applicable

8.0 Study Population

8.1 Inclusion Criteria:

- Ages 12 to $\leq$ 20 years at study entry
- Obesity (BMI $\geq$ the 95th percentile for age and sex)
- HgbA1c $\geq$ 6.5% at type 2 diabetes diagnosis
- Negative diabetes auto-antibodies
- English-speaking
- For participants of child-bearing potential: when sexually active, agreement to use two forms highly effective contraception (oral contraceptive pill, IUD, implant, and/or condoms) during study participation

8.2 Exclusion Criteria:

- Pregnancy or lactation
- Newly-initiated or change in dose of weight altering medication within past 6 months, including SGLT-2 inhibitors, DPP-IV inhibitors, liraglutide 1.8 mg and exenatide ER
- Current or recent (< six months prior to enrollment) use of anti-obesity medication(s) defined as orlistat, phentermine, topiramate, combination

PHN/TPM, semaglutide, and/or combination naltrexone/bupropion (monotherapy use of naltrexone or bupropion is not an exclusion)

- Current use of sulfonylureas
- Previous metabolic/bariatric surgery
- Current use of a stimulant medication
- History of glaucoma
- Current or recent (<14 days) use of monoamine oxidase inhibitor or carbonic anhydrase inhibitors
- Known hypersensitivity to sympathomimetic amines
- Any history of treatment with growth hormone
- Any history of bulimia nervosa
- Major psychiatric disorder as determined by the local medical monitor
- Unstable and clinically-diagnosed (defined as documented in the medical record, if available) depression or PHQ-9 score $\geq$ 15
- Any history of active suicide attempt, a "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSR, or a "yes" to answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS
- History of suicidal ideation or self-harm within the previous 30 days or a "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS and the ideation or behavior occurred within the past month.
- Current pregnancy or plans to become pregnant during study participation
- Current tobacco use
- ALT or AST >/= 3 times the upper limit of normal
- Moderate (Child-Pugh score 7-9) or severe (Child-Pugh score 10-15)
- Bicarbonate <18 mmol/L
- Moderate (creatinine clearance [CrCl] greater than or equal to 30 and less than 50 mL/min) or severe (CrCl less than 30 mL/min) renal impairment
- History of seizures (with the exception of febrile seizures)
- BP for ages 13 and older of $\geq$ 130/80 on 3 separate measurements and for age 12 $\geq$ 95th percentile on 3 separate measurements
- HR ≥120 bpm on 3 separate measurements
- History of structural heart defect or clinically significant arrhythmia
- Diagnosed monogenic obesity
- Any history of cholelithiasis
- Any history of nephrolithiasis
- Clinically diagnosed hyperthyroidism
- Untreated thyroid disorder or TSH below the lower laboratory limit of normal

- Any disorder, unwillingness, or inability, not covered by any other exclusion criteria, which in the investigator's opinion may put the participant at risk.

8.3 Visit Detail:

Screening Visit: After explaining the study in detail, written parental consent and assent will be obtained. If the participant is ≥18 years of age, the participant consent will be obtained. Potential participants will then undergo screening for inclusion and exclusion criteria (physical exam with height and weight for BMI calculation, Tanner staging for pubertal status. Screening lab [AST, ALT, INR, TSH, bilirubin, albumin, basic metabolic panel will be drawn at this visit and reviewed before setting up the baseline visit. INR, bilirubin, and albumin will be used to determine a Child-Pugh score for hepatic impairment for eligibility. Urine pregnancy test for participants of child-bearing potential will be obtained. BP and HR will be taken. Contraceptive counseling will be provided. The PHQ-9 and C-SSRS will then be completed. All other co-administered medications will be assessed. Participants will then have their medical and medication history collected and demographics collected.

Baseline Visit: Participants who meet eligibility criteria will return for a baseline visit within 4 weeks of the screening visit. Participants will have a physical examination, their height and weight will be measured and their blood pressure and heart rate will be taken. An EKG will be done, and contraceptive counseling will be given. Participants will complete the EDE-Q, and PedsQL. Their daily insulin and metformin doses will be reviewed if applicable. Participants will be instructed how to place and replace a CGM as well as swipe and upload data. The participant will have the OGTT testing and the plasma glucose levels, c-peptide levels and insulin levels taken at outlined timepoints as well as baseline lipid profile, and vitamin D level be drawn at time 0. Approximately 2 tablespoons of blood will be drawn at the visit. The participant will also have an iDXA for total body fat, visceral fat and bone mineral density calculations. Lifestyle management counseling will be given. The participant will then be randomized to receive either PHN/TPM or placebo and will be instructed on how to take the study medication. The participant will be provided with a Bluetooth scale for use at home and to transmit weights to the study team, with a water bottle to encourage water intake and with a drawstring bag to carry the study items.

Weeks 4, 8, 16, 20, 28, 32, 40, 44 and 48: At these timepoints the study staff will review the CGM data, and the participant may be contacted via telephone about adjusting their insulin or metformin dose. Participant will also present to the DCRU to collect study medication as well as upload CGM data if they are unable to do so from home and they will be given new CGM sensors. Monthly urine

pregnancy test results and contraceptive counseling if applicable will also done when the patient collects their study medication. If participants are able to upload CGM at home, then after week 24, a 2-month supply of study drug and CGM sensors and 2 urine pregnancy tests will be given to participants at visit 24 and a 3-month supply of study mediation and CGM sensors and 3 pregnancy tests will be given at visit 36. Study coordinator will then only do a telephone visit for weeks 28, 32, 40, 44, and 48 to review adverse events, home weight, and results of urine pregnancy test.

Week 12 and Week 36: Visits at these timepoints will be conducted at the CRU. Vital signs and weight will be collected. Participants will be asked about any adverse events they have experienced. Contraceptive and lifestyle management counseling will again be given and a pregnancy test will be performed. Participants will have a physical examination and pubertal assessment. Approximately one teaspoon of blood will be drawn for a hemoglobin A1c. Patients will also complete the EDE-Q, PHQ-9, and C-SSRS. Participants will be provided with new CGM sensors and study Medication bottles will be collected and pills counted by the study team to assess compliance. At the Week 12 visit, the pill count will be conducted by a team member not involved in the study so that the study blind is not broken.

Week 24 and Week 52: Participants will present for an in-person visit for a physical examination. Tanner staging, height and weight measurements will be collected. Vital signs (BP and HR) will also be collected. Contraceptive counseling and lifestyle management will again be given. Participants will be asked about adverse events that they have experienced. Blood will be drawn for a hemoglobin A1c, basic metabolic panel, lipid profile, and a Vitamin D 25. A review of the participants' daily insulin doses will be reviewed. Any co-administered medications will be discussed. Participants will have the OGTT testing and blood will be collected at the outlined timepoints for plasma glucose levels, c-peptide levels and insulin levels. Approximately two tablespoons of blood will be drawn at the visit. Participants will be asked to complete the EDE-Q, PedsQL, PHQ-9 and C-SSRS evaluations. Urine pregnancy test will be done and reviewed if applicable. An iDXA for total body fat, visceral fat and bone mineral density will be conducted. The participant will have their CGM data reviewed and new CGM sensors will be provided at week 24. The participant's insulin dose will be reviewed and their adherence to the study medication will be assessed. Study medication will be distributed for week 24. Instructions on how to down-titrate off the study medication will be done on week 52. Participants who elect to upload their CGM data remotely before the visit may elect to receive study medication, home urine pregnancy tests, and sensors to last them for the remainder of the study.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

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

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

9.2 Additional Safeguards:

Minor children will be enrolled in this study and will be asked to sign an assent form after their parents or legal guardian(s) sign a parental consent form. Legal guardians will be asked to provide proof of their status. If a minor child turns 18 while they are participating in the project, they will be asked to sign an adult consent form and HIPAA authorization at their next scheduled visit to indicate their willingness to stay in the study.

A parental consent form in Spanish has been created as a number of our participant children may be bilingual, but their parent may not be as comfortable with speaking English.

9.2 Local Number of Participants to be Consented:

We plan to enroll 30 participants into this pilot study.

10.0 Local Recruitment Methods

10.1 Recruitment Process:

We will work with Fairview Research Administration to identify potential participants who have not opted out of hearing about research projects and send

them a letter. Interested participants will be asked to contact the study team and up to three follow-up phone calls will be made by study staff if no initial response is received. We will also reach out directly to the patient's primary care provider or primary diabetes provider to inform the provider that their patient is possibly eligible for this study and provide them with a flyer for the patient. The patient can then contact the research coordinator directly or give verbal permission to be contacted.

Children's Minnesota will also send out recruitment letters to their patients.

10.2 Identification of Potential Participants:

Potential participants may self-identify by calling the study coordinator after receiving a recruitment letter (described above). Additionally, Dr. Bensignor may approach potential participants that she sees as part of standard care who may qualify for the project and inquire about their willingness to learn more.

10.3 Recruitment Materials:

A recruitment letter will be used to recruit potential participants. A recruitment flyer with study information will be given to patients in T2D clinic.

Endocrinologists within Park Nicollet and Children's will also be provided with a flyer to provide to interested patients who are seen in their clinic and will send out recruitment letters.

10.4 Payment:

Participants will be compensated for the study items that they complete. Participants can earn a total of $2265. The amount to be earned is broken down as follows:

- Screening visit $75
- Baseline visit: $100
- Week 4: $20 for review of CGM data
- Week 8: $20 for review of CGM data
- Week 12: $115 ($95 for the visit and blood draw, $20 for CGM review)
- Week 16: $20 for review of CGM data
- Week 20: $20 for review of CGM data
- Week 24: $120 ($100 for in-person visit and $20 for review of CGM data)
- Week 28: $20 for review of CGM data
- Week 32: $20 for review of CGM data
- Week 36: $115 ($95for the visit and blood draw, $20 for CGM review)
- Week 40: $20 for review of CGM data
- Week 44: $20 for review of CGM data
- Week 48: $20 for review of CGM data

- Week 52: $120 ($100 for in-person visit and $20 for review of CGM data)
- Swiping of the Libre CGM: $2/swipe (participants will be asked to swipe twice per day ($4 maximum per day, or $120 for a full month of swiping twice per day). For participants on the Dexcom G7, the data retrieval is automatic (swiping is not required) and participants will receive $4/day for each day the CGM is worn (maximum of $120 for each month).

The Greenphire ClinCard will be used for all compensation.

11.0 Withdrawal of Participants

11.1 Withdrawal Circumstances:

Participants who ask to be withdrawn from the project will have their request honored. Participants may be asked to come to one final study visit for a physical examination and hemoglobin A1c measurement for safety, if the PI thinks that this is required, and discuss how their insulin should be adjusted after taking PHN/TPM or placebo is stopped.

Participants who are not uploading their CGM data may be withdrawn from the study at the PI's discretion.

11.2 Withdrawal Procedures:

Participants who wish to withdraw from the study will be allowed to do so. They will also be offered to stop taking the study medication/placebo but continue with the visits.

11.3 Termination Procedures:

Participants who withdraw from the study will not have additional study information collected. Data that had been collected prior to their withdraw will still be reviewed and utilized.

12.0 Risks to Participants

12.1 Foreseeable Risks:

Expected Adverse Events

PHN/TPM: Adverse events will be reviewed and documented at each study visit and phone call (monitored monthly throughout the study). Participants will be instructed to contact study staff immediately if any adverse event is experienced. Overall, the safety profile of PHN/TPM has been demonstrated to be acceptable in adults, with paresthesia (mild tingling in the extremities), dysgeusia (altered taste), insomnia, constipation, and dry mouth as the most commonly reported (incidence ≥5%). Of note, topiramate use during the first trimester of pregnancy is associated with an increased risk of oral clefts in the fetus. A basic metabolic panel at weeks 0, 24, and 52, and urine pregnancy test (for persons of child-

bearing potential) will be performed monthly. We will require all sexually active participants who are of child-bearing potential to confirm use of at least two forms of effective contraception. In addition, we will monitor for potential changes in depression, anxiety, suicidal behavior and ideation, acute myopia and secondary angle closure glaucoma, mood and sleep disorders, cognitive impairment, metabolic acidosis, kidney stones, and elevated creatinine. Participants will be asked to increase their fluid intake in order to help decrease the concentration of substances involved in kidney formation. Topiramate can increase the risk of suicidal ideation and behavior. Participants will be screened for depression with the PHQ-9 and suicidal ideation and behavior with the C-SSRS. If any questionnaire reveals suicidal behavior or ideation with some intent to act on it, then test results will be confirmed by the PI prior to discharging the subject from the study. Study medications will be weaned off if there is suicidal behavior or ideation with some intent to act on it.

Insulin: Participants may already be on insulin therapy upon enrollment in the study or it may be used to treat hyperglycemia. There is a risk of bruising, bleeding and infection associated with insulin injection. Hypoglycemia may also occur with insulin use, and this risk increases with weight loss. Participants who are on insulin will be trained on the signs of low blood sugar and how to treat an episode of hypoglycemia. Hypoglycemic episodes will be documented by CGM and reviewed monthly, or sooner if needed. Doses of metformin and insulin (if applicable) will be down titrated to help prevent further hypoglycemia.

Metformin: Participants may already be on metformin therapy upon enrollment into the study or the metformin dose may be titrated during the course of the study. Side effects of metformin include diarrhea, bloating, nausea and vomiting, which are usually self-resolving. Side effects will be reviewed at each study visit and metformin can be down titrated or discontinued if warranted by the PI. Participants can be on either immediate-release or extended-release formulations of metformin.

OGTT: There is a minimal risk of bruising, bleeding and infection associated with the blood draw and peripheral IV placement for the OGTT. There is also a risk of temporary hyperglycemia during the testing.

Continuous Glucose Monitoring: There is a minimal risk of bruising, bleeding, and infection associated with placement of the CGM device. Participants will be trained how to apply the device at baseline. In general, CGM is well tolerated and accepted. A diabetes clinical nurse will be available to participants to help address any issues with CGM placement and maintenance remotely.

Screening and monitoring labs: The risks of drawing blood for this test include bruising, bleeding and infection at the site where the needle enters the skin. On rare occasions, fainting may occur.

Dual Energy X-ray Absorptiometry (iDXA): The iDXA scans involve exposure to a very low dose of ionizing radiation to generate their picture. The average amount of radiation that the average person would receive from the iDXA scans in this study is less than 1% (3 mrem) of that received from natural sources of radiation by a Minnesota resident in one year (300 mrem).

Risks of Questionnaires, EDE-Q, PHQ-9, C-SSRS, PedsQL: Individuals may feel self-conscious or nervous about answering these questions. However, the risk of being able to provide an intervention if an individual develops unhealthy eating habits or suicidal ideations is felt to outweigh the risks.

There is always a risk of a breach in confidentiality associated with the use of data that can be linked back to individuals. The study team will utilize password protected programs in which to enter data and study data in paper form will be kept in offices that are locked when unattended.

12.2 Reproduction Risks:

All participants of child-bearing potential who are sexually active must agree to use two forms of birth control during their time in the study. Participants of childbearing potential will have urine pregnancy monthly, during a study visit or medication pick-up. Participants of childbearing potential who are sexually active will be instructed to use a highly effective birth control method. Participants of childbearing potential who think that they may be pregnant will be asked to stop taking the study medication and call the study doctor as soon as possible.

12.3 Risks to Others:

Not applicable.

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

12.5 Definition of Serious Adverse Events (SAE):
A SAE is an AE that fulfills at least one of the following criteria:

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

12.6 Classification of an Adverse Event

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

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

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

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

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

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

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

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

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

The PI will notify the IRB of any SAE that meets the definition of being unexpected (in terms of nature, severity or frequency), that is related or possibly related to participation in the research and places the subject or others at increased risk of harm per current IRB policy within five days of knowledge of the event. The PI will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected SAE as soon as possible, but in no case later than seven calendar days after the PI's initial receipt of the information in compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. Non-fatal or non-life-threatening SAEs will be reported to the FDA no later than 15 days after the PI's initial receipt of the information. The PI will report any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to the FDA no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. The PI will also submit annual progress reports within 60 days of the anniversary of the date that the IND becomes active.

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

13.0 Potential Benefits to Participants

13.1 Potential Benefits:

The interventions and outcome measures in the proposed study, with the exception of PHN/TPM, presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical situations and typical clinical care. Since data from clinical trials in adults and adolescents with obesity have demonstrated reduction in BMI with PHN/TPM treatment, it is anticipated that PHN/TPM will provide greater BMI reduction and therefore improved insulin sensitivity and glycemic control than standard T2D care.

14.0 Statistical Considerations

14.1 Data Analysis Plan:

There are 3 analysis populations planned, Intention-to-treat (ITT) will include any participant randomized according to their treatment assignment. Per-protocol (PP) will include those without protocol violations and who were compliant (≥80%) with their treatment assignment measured by medication log and medication collection. The safety population will include all who receive treatment, according to treatment received.

14.2 Power Analysis:

Percent change in BMI from baseline (randomization) and 6 months will serve as the primary outcome for which the sample size determination is based. Sample size was based on feasibility. We consider variability estimates from our previous experience with anti-obesity medication trials in the adolescent population, suggesting a standard deviation of approximately 8.9 and a conservative correlation between baseline and follow-up of 0.75. Based on an overall sample size of 30 (15 in each of two treatment arms) and type I error of 0.05, we will have 80% power to detect treatment difference of 6%. This percent change in BMI is clinically significant and similar to other results found in the previous PHN/TPM trials.[6,35] We also appreciate degree of attrition may be unavoidable. In the event of 10% attrition (recent experience for our study group in a trial involving a similar adolescent population with severe obesity), we will have 80% power for a treatment difference of 6.3%.

14.3 Statistical Analysis:

Descriptive analyses of baseline characteristics and outcomes will include means and standard deviations, median and range for continuous variables and frequencies for categorical variables. Treatment adherence will also be evaluated by the methods described above. Safety analyses will be primarily descriptive reporting the number and percentage of adverse events. All safety outcomes will be evaluated and monitored throughout the trial. Confidence intervals (CIs) and p-values will be based on robust variance estimation. Statistical significance will be considered as $p<0.05$.

Aim 1: The primary analysis will be conducted using the ITT population to compare the mean BMI percent change (primary outcome measure) from randomization to 6 months of follow-up between the groups, adjusted for BMI at randomization for added precision.[38-39] We hypothesize that with participants treated with PHN/TPM will demonstrate greater BMI percent change compared to controls at 6 months. Supportive analyses using the PP population will also be conducted along with consideration of adjustment for residual imbalances

between treatment groups after randomization (e.g., in sex as a biological variable). Longitudinal analyses will also be conducted, incorporating the multiple time points through the open-label extension (6 months to 12 months follow-up) during which these BMI measurements will be obtained. This will examine durability of changes observed over the masked portion of follow-up, as well as provide additional safety information. Supportive analyses using the PP population will also be conducted.

Aim 2: Secondary outcomes will be analyzed in the same fashion as the primary endpoint wherein analyses will be adjusted for values at randomization. Outcome measures for Aim 2 are c-peptide index ($\Delta C_{30}/\Delta G_{30}$), insulin sensitivity (1/fasting insulin), β-cell function relative to insulin sensitivity (oral deposition index [oDI]), A1c (%), and total daily insulin dose (units/kg/day). We hypothesize that participants treated with PHN/TPM will demonstrated improved insulin sensitivity and β-cell function compared to those assigned to placebo as measured by OGTT, A1c and total daily insulin doses. Complementary secondary analyses will also be conducted for each secondary outcome as described for the primary outcome.

Exploratory Aim: In an exploratory fashion, we will compare the mean change in total body- and visceral fat (expressed as percent and absolute) and cardiometabolic measures from randomization to 6 months of follow-up between the groups, adjusted for randomization values for added precision.

14.4 Data Integrity:

Despite efforts, it is possible that some data will be missing, which could limit the interpretation and generalizability of results. If the data are missing at random, conditioned on measured covariates, then supplementary analyses adjusting for these covariates will produce unbiased results. For potential missing data mechanisms beyond measured covariates, we will examine the extent to which results may be affected. Imputation techniques will be considered for missing data issues (e.g., multiple imputation). In particular, for the primary analysis we will use a last observation carried forward approach for participants on whom we do not have a final measurement. Additional complementary analyses will incorporate Markov Chain Monte Carlo (MCMC) multiple imputation to handle missing data. The imputation model will be stratified by treatment group and include baseline values at randomization. Additional variables for possible inclusion in the model include age, race, sex, and Tanner stage, though unlikely to be more than one in any single model due to sample size limitations. MCMC imputation will be used to estimate treatment group differences, 95% confidence intervals and P values; observed data will be used to estimate within treatment group changes. If the analyses with ad without multiple imputed values differ

substantially, then exploratory analyses will be performed to evaluated factors that may have contributed to the differences. Secondary endpoints will be handled similarly.

15.0 Health Information and Privacy Compliance

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

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

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

Appropriate Use for Research:

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

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

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

☒ I will collect information directly from research participants.

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

☒ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

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

☐ I will receive a limited data set from another institution

☐ Other.

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

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

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

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

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

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

☒ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.
Subjects will receive telephone calls, virtual visits through the AmWell Platform, and emails regarding the study. The detail of telephone calls that this study requires is outlined in the consent form. Emails that contain PHI will be sent to the subject/parent in a secure, encrypted manner.

15.6 Explain how the research team has legitimate access to patients/potential participants:

This has been explained in other sections of the protocol.

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

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

☒ Store ☐ Analyze ☐ Share

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

☐ Store ☐ Analyze ☐ Share

☒ In REDCap (recap.ahc.umn.edu)

☒ Store ☒ Analyze ☒ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu) OnCore will serve as the EDC for the project

☐ Store ☐ Analyze ☐ Share

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

☒ Store ☐ Analyze ☒ Share

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

☐ Store ☐ Analyze ☐ Share

☒ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☒ Store ☐ Analyze ☒ Share

☐ Other. Describe:

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

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

☐I will use a desktop or laptop not previously listed

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

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

15.8 Consultants. Vendors. Third Parties. The CGM that is provided to the participant in the Discovery Clinic can collect and transmit data. The participant can choose, via the app, to share the data with the study team.

15.9 Links to identifiable data:
Absolute confidentiality will be maintained. All data will be stored in locked offices and will not be released without consent of participants. Data to be used in scientific presentations or publications will not contain participant identifiers.

15.10 Sharing of Data with Research Team Members.

Study team members will have access to the data shelter, REDCap, Box and to OnCore.

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

16.0 Confidentiality

16.1 Data Security:

Absolute confidentiality will be maintained. All data will be stored in locked offices and will not be released outside of the study team without consent of the participant. Data that is collected will be entered into OnCore, REDCap, and Box which are accessible only by the study team. Data to be used in scientific presentations or publications will not contain participant identifiers. As this study is funded by the National Institutes of Health, a Certificate of Confidentiality will be in place to help protect the research data from disclosure to outside entities.

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

17.1 Data Integrity Monitoring.

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

17.2 Data Safety Monitoring.

Responsible Individual: Dr. Bensignor will be responsible for data and safety monitoring and will review all adverse events and serious adverse events regularly throughout the trial. A data and safety monitoring board (DSMB) has been established and includes one adult endocrinologist, one pediatric endocrinologist and one biostatistician. DSMB members are not to be affiliated with the study. The DSMB will meet regularly (frequency to be determined by the DSMB) during the trial to review data and evaluate participant safety. A charter for the DSMB to outline the responsibilities and procedures for the conduct of the monitoring board has been developed and approved by its members along with a

plan for frequency of data review prior to the commencement of the trial. Review materials for the DSMB will be prepared and presented by the study biostatistician, Dr. Kyle Rudser (co-mentor). A report from each meeting will be sent to the PI and her mentorship team advising on the continuation of the study and any suggestions for trial improvement. This report will also be sent to the assigned NIH Program Director and the University of Minnesota Institutional Review Board (IRB). An important charge of the DSMB will be to closely monitor progress and timelines related to recruitment goals, fidelity to the protocol (e.g. regularly review the number and types of protocol deviations), as well as monitor the quality and integrity of the data. The DSMB will communicate any concerns relevant to these issues of trial conduct to the PI and her mentorship team and note specific recommendations for improvement in the meeting report.

Overall Framework: There will be a specific and comprehensive plan for monitoring the safety of participants and the integrity of the study data, which will include careful assessment and appropriate reporting of adverse events and use of a DSMB as described above. Adverse events will be monitored closely, and participants will be provided with information about the risks/side effects of the study medication (PHN/TPM) and study procedures. Participant safety is the study team's utmost priority. Accordingly, Dr. Bensignor will involve a team of experienced clinical investigators who will adhere to the standards of the International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable U.S. Code of Federal Regulations (CFR), and the protocol, which will be approved by the University of Minnesota IRB. Adverse events and protocol deviations will be reviewed by Dr. Bensignor, the clinical nurse, and research coordinator after each study visit. Additionally, Dr. Bensignor will receive guidance and regulatory support from her mentorship team and the Center for Pediatric Obesity Medicine's Regulatory Specialist, Lisa Hostetler, CCRC.

Participant Safety: At the outset, participant risk will be minimized by study team adherence to exclusion and inclusion criteria during screening. The proposed research will expose the participants to a minor increase over minimal risk. The exclusion criteria include, but are not limited to, contraindications to PHN/TPM. Participant assessments will be done at study visits every three months. Participants and their parent/guardian (if < 18 years) will be provided with contact information for Dr. Bensignor (study PI), clinical nurse, and the research coordinator with explicit instructions to contact the study team in the event of emergencies.

Participant Stopping Rules: In the event that a participant has a serious adverse event that is deemed related to the study medication and/or procedures by the PI, the participant will be required to immediately discontinue the intervention. The overall study may be stopped at any time at the request of the PI and/or the DSMB. Participants will be removed from the study if suicidal ideation, excessive

weight loss, or disordered eating is present at any time during the trial or if any clinically significant changes (at the discretion of the PI) in mood and/or depression are observed. If the ratio of participants on medication vs. placebo developing a serious adverse event requiring withdrawal exceeds 4:1 (after ≥ 50% enrollment and a minimum of 5 total events, regardless of group assignment), the trial will be stopped. Patients will be instructed that they may withdraw from the study at any time and for any reason without impact on their typical clinical care.

Study Integrity: As stated above, the study will undergo annual monitoring of the facility, staff, and study documents by clinical research associates of the University of Minnesota Clinical Trials Monitoring Service. Monitoring staff will provide a summary report to Dr. Bensignor and her mentorship team after each site visit. If necessary, corrective action plans will be devised and implemented by Dr. Bensignor to address deficiencies.

The PI and research coordinator will generate administrative reports describing the study progress, subject recruitment, subject demographic data, subject status, compliance with inclusion/exclusion criteria, and adverse events. The study statistician and co-mentor, Dr. Rudser, will review data on adverse events, and notify Dr. Bensignor if any events pose statistical concern or occur in disproportionate numbers throughout the intervention groups. Further, the PI and research coordinator will regularly monitor data for accuracy.

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy: see HIPCO ancillary review

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

19.0 Compensation for Research-Related Injury

19.1 Compensation for Research-Related Injury:

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

19.2 Contract Language:

Not applicable.

20.0 Consent Process

20.1 Consent Process (when consent will be obtained):

Assent and parental consent will be obtained by a study investigator or the study coordinator after explaining the entire study in detail, asking the participant and the parents/guardians to explain the purpose, risk and benefits, and other details of the study, and giving the participant and parents/guardians an opportunity to ask questions. A copy of the signed assent and parental consent forms will be given to the participants and parents/guardians. For individuals who are 18 years of age or older at study entry, the same process as described above will happen, but the participant will sign a consent form.

In an effort to minimize participant face-to-face time due to COVID-19 concerns, the consent discussion and process may be done virtually. This will be offered to be conducted via Zoom for families with a computer and an internet connection and the Zoom connection will be encrypted so that it will be private. The study coordinator will mail two copies of the parental consent, assent and HIPAA forms and will review the study, review the documents and address any concerns that the parent or participant may have. If the participant and parent agree to enroll in the study, they will be asked to sign both copies of each of the forms and return one set of originals via mail to the study coordinator for placement in the participant file. We anticipate that there will be a date discrepancy between when the participant and parent sign the forms and the date the form is returned to the study coordinator and a notation will be made about the discrepancy.

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

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

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

Not applicable.

20.4 Non-English Speaking Participants:

We do not plan on enrolling non-English speaking participants at this time.

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

This study will enroll participants who are under the age of 18 and they will be asked to sign an IRB-approved assent form. Their parents/guardians will be asked to sign a parental consent form.

Individuals who sign an assent form but turn 18 during the course of the study will be asked to sign a consent form and HIPAA to indicate that they are still willing to

participate in the study. A copy of the signed consent form will be given to the participant.

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

Not applicable.

20.7 Adults Unable to Consent:

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

21.0 Setting

21.1 Research Sites:

- Delaware Clinical Research Unit
- Clinical Research Unit

21.2 International Research:

Not applicable.

22.0 Multi-Site Research

Not applicable.

23.0 Coordinating Center Research

Not applicable.

24.0 Resources Available

24.1 Resources Available:

The Delaware Clinical Research Unit (DCRU) is a research unit at the University of Minnesota that includes a waiting room, playroom, exam rooms, laboratory processing facility, temporary freezer and refrigerator storage, physician dictation rooms, and an iDXA. The staff who will be performing the phlebotomy for this project have CITI and HIPAA training, have been trained in proper phlebotomy techniques and have bloodborne pathogen training and hazardous sample shipping training. The personnel who run the iDXA also have training certification on file.

The Clinical Research Unit (CRU) is a joint venture of MHealth, Fairview, the University of Minnesota and UM Physicians. The unit is equipped for research as well as standard medical care and is available for overnight stays, as needed.

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