USE OF PHARMACOTHERAPY TO IMPROVE WEIGHT LOSS IN EARLY NON-RESPONDERS TO BEHAVIORAL TREATMENT

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Investigational Product:	Phentermine 15.0 mg
Protocol Number:	Application number 1K23KD116935-01A1
IRB Number:	
IND/ IDE Number:	Not applicable
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List of Abbreviations

AE: Adverse event

BMI: Body mass index

BT: Behavioral treatment for obesity

BT + M: Behavioral treatment plus medication with phentermine 15.0 mg

BT + P: Behavioral treatment plus placebo

CMP: Comprehensive metabolic panel

GLP-1: Glucagon-like-peptide-1

IDS: Investigational Drug Service (at Penn)

NP: Nurse practitioner

PYY: Peptide YY

RD: Registered dietitian

RRV_{food}: Relative reinforcing value of food

SAE: Serious adverse event

Study Summary

Title	Use of Pharmacotherapy to Improve Weight Loss in Early Non-responders to Behavioral Treatment
Short Title	Medication in BT Non-responders
IRB Number	
Phase	N/A
Methodology	Double blind, placebo-controlled randomized trial
Study Duration	4 years
Study Center(s)	Single-center

Objectives

Primary:

- Phase 1: To characterize satiety in early non-responders to behavioral treatment (BT). Lower satiety ratings, lower postprandial increases in GLP-1, and more rapid gastric emptying at baseline are hypothesized to predict percent weight loss from the start of the BT run-in (week -4) to randomization (week 0), as well as categorization as an early non-responder who lost < 2.0% of initial weight at randomization (co-primary outcomes).

- Phase 2: To test the effect of augmenting BT with the weight loss medication phentermine 15.0 mg (BT+M), compared to BT plus placebo (BT+P), on weight loss in early non-responders who lose < 2.0% of initial weight during a 4-week behavioral run-in. Percent weight loss from randomization to week 24 is the study's primary endpoint.

Secondary:

- Phase 1: To examine whether additional behavioral characteristics (higher fasting hunger, relative reinforcing value of food [RRV_{food}], and impulsivity) and neuropeptides (higher fasting ghrelin, lower fasting leptin, and lower postprandial changes in cholecystokinin and peptide YY) predict 4-week weight loss, as well as categorization as a non-responder during the BT run-in.

- To compare the portion of early non-responders who achieve a post-randomization loss of ≥ 5% and ≥ 10% of initial body weight with BT+M and BT+P.

- To compare non-responders treated with BT+M vs. BT+P in changes in hunger, satiety, RRV_{food}, and impulsivity between randomization and week 24.

- To explore differences in percent weight loss from randomization to week 24 between early non-responders treated with BT+M and early responders treated with BT alone.

Number of Subjects

150 subjects (180 in-person screenings to obtain 150)
60 subjects randomized to study medication(s)

Main Inclusion and Exclusion Criteria

Key Inclusion Criteria

1. BMI ≥ 31 kg/m² (or 28 kg/m^2 with obesity-related comorbidity)
2. Age ≥ 21 years and ≤ 70 years
3. Has a primary care provider (PCP) responsible for providing routine care
4. Plans to remain in the Philadelphia area for the next 9 months or more

Key Exclusion Criteria

5. Pregnant or nursing, or plans to become pregnant in the next 9 months.
6. Uncontrolled hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg)
7. Type 1 diabetes
8. Type 2 diabetes
9. A fasting blood glucose > 126 mg/dL(on second assessment after first elevated value, patients are excluded if they have both fasting blood glucose > 126 mg/dL and HbA1c ≥ 6.5)
10. History of cardiovascular disease (e.g., coronary artery disease, stroke, arrhythmias, congestive heart failure, or heart block greater than first degree)
11. Clinically significant hepatic or renal disease
12. Hyperthyroidism
13. Other thyroid disease, not controlled.
14. History of malignancy (except for non-melanoma skin cancer) in past 5 years
15. Narrow angle glaucoma
16. Presence or history of marked agitation
17. Current severe major depressive episode (BDI-II score ≥ 29), current active suicidal ideation, or history of suicide attempts within the past 5 years.
18. Any severity of thought or bipolar disorder, or bulimia nervosa.
19. Psychiatric hospitalization within the past 6 months
20. Self-reported alcohol or substance abuse within the past 6 months, including at-risk drinking (current consumption of ≥ 14 alcoholic drinks per week)
21. Past year history of drug abuse.
22. Use in the past 2 weeks of monoamine oxidase inhibitors.
23. Current use of serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, duloxetine, desvenlafaxine, milnacipran, levomilnacipran).
24. Use in past 6 months of medications known to induce significant weight loss (e.g., prescription weight loss medications) or weight gain (e.g., chronic use of oral steroids, second generation antipsychotics)
25. Loss of ≥ 5% of initial body weight within the past 6 months
26. History of (or plans for) bariatric surgery (e.g., roux en y gastric bypass, sleeve gastrectomy, gastric banding), endoscopic intragastric balloon, or aspire assist.
27. Inability to walk 5 blocks comfortably or engage in some other form of aerobic activity (e.g., swimming)
28. Known or suspected allergy to sympathomimetic amines or related products
29. The receipt of any investigational drug within 6 months prior to this trial
30. Previous participation in this trial (e.g., randomized and failed to participate)
31. Changes to any chronic medication (type or dosage) within the past 3 months.

	32. Any serious or unstable medical or psychological condition that, in the opinion of the investigator, would compromise the patient's safety or successful participation in the study
Investigational Product (drug, biologic, device, etc.)	
For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment	Phentermine 15.0 mg/day, provided in capsule form. (Study medication will be initiated at 8.0 mg/day for the first 2 weeks and increased to 15.0 mg/day thereafter.)
Duration of administration (if applicable)	24 weeks
Reference therapy	Placebo for phentermine
Statistical Methodology	All data will be analyzed under the intention-to-treat principle. Multiple regression and discriminant analysis will be used to examine phase 1 predictors of early weight loss with BT and categorization as a non-responder, respectively. To assess the primary phase 2 outcome of percent weight change by treatment group (among non-responders), a mixed effects model will be fit with treatment group (BT+P, BT+M) as a between-subjects factor and time (week) as a within-subjects factor to estimate and test group differences at week 24 (primary endpoint).
Safety Evaluations	Safety endpoints include physical examination, adverse events (AEs), and standard laboratory tests. In addition to assessment visits, randomized subjects will have a brief medical monitoring visit (10-15 minutes) with study staff (e.g., registered nurse) at week 2 (after initiation of the medication) and week 4 (after most subjects will have completed dose escalation) to monitor response to the medication. Study subjects will be asked whether there has been any change in their health or medications. Side effects will be queried during every study visit, and the study NP or physician will be available to assess the subject and evaluate and treat any adverse events. Subjects will be encouraged to contact study staff immediately should an AE occur between visits, and 24-hour contact information will be provided for study personnel and the study physician. If any AE requires treatment follow-up, subjects will be provided with appropriate referrals. Subjects will have fasting blood draws (comprehensive metabolic panel [CMP] and lipids) at screening, and at randomization and week 24. Vital signs (blood pressure and pulse) will be measured at screening and post-randomization weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24.

The principal investigator (PI, Dr. Tronieri) will be responsible for overseeing and monitoring the study. Safety and data quality monitoring will be performed on an ongoing basis by the PI and research coordinator, in consultation with Drs. Wadden and Berkowitz.

Data and Safety Monitoring Plan

A Safety Monitoring Committee consisting of a safety officer and data officer will provide additional study oversight. This team will include at least one external (non-Center) reviewer. The Committee will be responsible for executing the data safety and monitoring plan, monitoring trial safety and efficacy, and complying with Public Health Service reporting requirements. This team will meet prior to the start of recruitment to review the protocol, human subjects' protections, and plans for data and safety monitoring. They will then meet twice per year to review the study's progress and de-identified group-level data for differential rates in AEs and key outcomes

BACKGROUND AND STUDY RATIONALE

This study will be conducted in compliance with the protocol and in full accordance with Good Clinical Practice standards, all applicable University of Pennsylvania Research Policies and Procedures, and all applicable Federal and state laws and regulations including *45 CFR 46, 21 CFR Parts 50, 54, and 56.*

Introduction

A substantial minority of patients treated with behavioral treatment (BT) for obesity fail to achieve clinically meaningful losses of ≥ 5% of initial weight. Medications approved by the Food and Drug Administration (FDA) for weight management enhance average weight losses when combined with BT; however, their use among patients with suboptimal response to BT has never been tested in a randomized controlled trial. This study seeks to identify behavioral and biological phenotypes predictive of poor response to BT and test whether providing pharmacotherapy with phentermine 15.0, as compared to placebo, improves the induction of weight loss for subjects who lose minimal weight with 4 weeks of BT alone (a strong predictor of later failure to lose ≥ 5% of initial weight with that treatment).

1.1 Background and Relevant Literature

1.1.1 Obesity and Its Treatment.

Obesity, defined by a BMI ≥ 30 kg/m², is the most common nutritional disease in the United States, affecting about 36% of adults age 20 years and over. An additional 33% of American adults are overweight, as judged by a BMI of 25.0-29.9 kg/m². Obesity is associated with a number of co-morbidities including type 2 diabetes (70% of people with type 2 diabetes are obese) and cardiovascular disease.

Current treatment guidelines [e.g., 1] recommend that patients with obesity be offered comprehensive behavioral treatment that includes a reduced calorie diet, increased physical activity, and behavioral strategies to facilitate adherence to diet and activity goals. On average, patients achieve losses of 5-8% of initial weight with 6 months of high intensity BT (i.e., ≥ 14 individual or group sessions in 6 months). [1] (Providing more than 16 visits in 6 months [e.g., weekly visits] does not appear to significantly increase weight loss. [2]) A loss of ≥ 5% of initial weight is commonly used as a criterion for clinically meaningful weight loss and is associated with improvements in cardiometabolic risk factors. [3] However, 35-50% of patients fail to lose this amount in high intensity BT programs. [4, 5]

1.1.2 Non-response to BT.

Numerous studies have shown that slow early weight loss (e.g., < 0.5% of body weight per week) in the first 1-2 months of BT is a strong predictor of limited total weight loss after 6-12 months of treatment. [4, 6-13] Approximately one third of participants fail to lose ≥ 0.5% of body weight per week in the first month of BT, and the majority of these early non-responders do not achieve a loss of ≥ 5% body weight after 6 months of treatment (53-70%).[4, 7, 8]

1.1.3 Factors Influencing Weight Loss Success.

Obesity-related phenotypes, consisting of clusters of behavioral, psychological, and physiological characteristics, may facilitate or limit response to BT.[14, 15] The most consistent behavioral phenotypes associated with poor weight loss include low satiety and high hunger, [16-19] as well as a high reinforcing value of food [20, 21] and high impulsivity. [21-26] Lower satiety ratings after consuming a standard meal predict higher short- and long-term energy intake and less weight loss with BT. e.g. [16, 17, 27] Higher fasting hunger has also been associated with greater energy intake and poor weight loss [16, 18, 19]. A high relative reinforcing value of food (RRV_{food}) is associated with higher food intake and body weight. [27-31] Delay discounting (DD) is conceptualized as an aspect of impulsivity that reflects difficulty with inhibiting responses to rewarding stimuli.[24, 28, 32] In a meta-analysis, individuals with a steeper rate of DD, or those with the greatest preference for immediate rewards over larger, delayed rewards, were more prone to obesity.[24] Individuals who have both a high RRV_{food} and steep DD may have the greatest difficulty regulating their intake in order to lose

weight,[21, 28, 32-34] because weight loss participants are asked repeatedly to choose low-calorie foods that will produce long-term weight loss over palatable high-calorie foods that offer a more immediate reward.[26, 28]

Behavioral phenotypes are presumed to be linked to biological mechanisms that control hunger and food responsiveness. [20, 26, 35-38] Several neuropeptides are involved in the detection of long- (e.g., leptin) and short-term energy needs (e.g., glucagon-like-peptide-1 [GLP-1], ghrelin, insulin, peptide YY [PYY]), and they influence perceived palatability and reward-motivated eating (e.g., GLP-1, leptin, ghrelin). e.g. [39, 40] The rate of gastric emptying both influences and is influenced by several of these neuropeptides and may also affect food consumption and body weight.[39, 41-43] However, few studies have examined whether pre-treatment neuropeptide levels or gastric emptying predict weight loss with BT. The majority of these studies have examined the role of pre-treatment leptin and ghrelin levels in predicting weight loss, with mixed success.[39, 44-49]

Individual predictors typically explain only a small amount of the variance in weight loss outcomes, suggesting high inter-individual variability in mechanisms of non-response.[50] In some cases, obesity phenotypes may be mutually exclusive (e.g., high hunger and low satiety), while in others, the combination of several traits may best characterize a mechanism of non-response (e.g., high RRV_{food} and high impulsivity). The ability of most studies to detect distinct phenotypes that predict weight loss has been limited by their inclusion of only a small number of self-report measures.[14, 50, 51] Simultaneously examining multiple behavioral traits using laboratory-based assessments, along with neuroendocrine biomarkers and gastric emptying, may enhance our ability to identify phenotypes associated with poor response to BT. Better characterizing these non-responders will in turn facilitate the development of tailored treatments that can address different biopsychosocial barriers.

1.2 Treating BT Non-responders.

In addition to identifying mechanisms of non-response, it is important to evaluate whether alternative treatments improve the weight losses of BT non-responders. Several researchers have recommended that non-responders be provided with a different treatment method as early as possible, rather than spending ≥ 6 months in a treatment program that is unlikely to facilitate a clinically significant weight loss. [4, 6-9] Early non-responders to BT are also likely to become discouraged about reaching their desired weight loss goals and are more likely to drop out of treatment. [10, 52, 53]

Several studies have examined the efficacy of stepped-care approaches in which BT is intensified for patients who do not meet early weight loss milestones. The baseline treatment offered in these programs has been of low intensity, consisting of self-help [54], internet-based BT [55], or monthly BT visits [56], and treatment has primarily been intensified by increasing provider contact. The effect of offering a categorically different treatment to early non-responders in an intensive BT program has not been tested in an RCT.

1.2.1 Pharmacotherapy for Weight Management.

Expert panels recommend that individuals with a BMI ≥ 30 kg/m^2 (or BMI ≥ 27 kg/m^2 with comorbidity) be offered adjunctive treatments such as FDA-approved medications for chronic weight management if they are unable to lose weight or sustain weight loss with BT alone. [1, 57] Multiple studies have demonstrated that combining BT with medication produces greater weight loss (and reduces weight regain), compared to BT with placebo. [e.g., 58-68] Wadden and colleagues [59] have shown that the effects of BT and medication are additive. Participants prescribed medication alone (sibutramine 10-15 mg/day) lost 5 kg of initial weight at 1 year, those provided high-intensity BT alone lost 6.7 kg, and those given the combination of these two therapies lost 12.1 kg. [59]

Phentermine 15.0 mg.

Phentermine hydrochloride is a sympathomimetic amine thought to reduce appetite and food intake by increasing norepinephrine and possibly catacholamine levels in the hypothalamus. Phentermine was approved by the Food and Drug Administration (FDA) in 1959 for “short-term” use, commonly interpreted as 12 or fewer weeks. In 2012, the FDA approved the combination of phentermine (7.5 – 15.0 mg/d) plus topiramate for long-term weight management (e.g., ≥12 months). Phentermine (monotherapy) is the most widely used weight loss medication in the U.S. and is frequently prescribed in clinical practice for periods

longer than 12 weeks. [69-71] The FDA did not require an Investigational New Drug (IND) application for the use of phentermine in the present study. Patients without diabetes achieve average placebo-subtracted weight losses of 4.0 to 7.4 kg with 12 to 28 weeks of treatment with phentermine (15.0-30.0 mg/d). [72-77] In a recent representative study, subjects who received BT plus phentermine 15.0 mg/d lost 6.0 kg (6.1% of initial weight), whereas those who received BT with placebo lost 1.5 kg (1.7% of initial weight). [77]

Higher fasting hunger and lower dietary restraint have been shown to predict a greater likelihood of achieving a 5% weight loss among patients treated with 8 weeks of phentermine. [18] In another study, low satiety was associated with reduced weight loss at 2 weeks in patients assigned to placebo, but with greater weight loss in those who received phentermine-topiramate. [78] These findings suggests that phentermine will be particularly beneficial for individuals with the very phenotypes (e.g., high hunger, low satiety) that may predict non-response to BT.

Studies of the efficacy of weight loss medication have either initiated medication simultaneously with low- to moderate-intensity BT, [61, 63-65, 68] or have only randomized patients to medication or placebo if they succeeded in achieving a certain weight loss criterion (e.g., 5%) during an initial BT run-in. [58, 66, 67, 79] Remarkably, the recommendation to offer weight loss medication to individuals who are unable to successfully lose weight with BT alone has not been tested.

2 Study Objectives

This study consists of two phases. Phase 1 will evaluate obesity-related behavioral and biological characteristics as potential mechanisms of non-response to BT. Phase 2 is a double-blind, placebo-controlled, RCT to test whether augmenting BT with weight loss medication improves 6-month weight loss, as compared to BT with placebo, in subjects identified as early non-responders to 4 weeks of individual behavioral weight control.

2.1 Primary Objective of Phase 1

- To characterize satiety in early non-responders to behavioral treatment. Lower satiety ratings, lower postprandial increases in GLP-1, and more rapid gastric emptying at baseline are hypothesized to predict percent weight loss from the start of the BT run-in (week -4) to randomization (week 0), as well as categorization as an early non-responder who lost < 2.0% of initial weight at randomization (co-primary outcomes).

2.2 Secondary Objectives of Phase 1

- To examine whether additional behavioral characteristics (higher fasting hunger, relative reinforcing value of food [RRV_{food}], and impulsivity) and neuropeptides (higher fasting ghrelin, lower fasting leptin, and lower postprandial changes in insulin and PYY) predict 4-week weight loss, as well as categorization as a non-responder during the BT run-in.

2.3 Primary Objective of Phase 2

- To test the effect of augmenting BT with the weight loss medication phentermine 15.0 mg (BT+M), compared to BT plus placebo (BT+P), on weight loss in early non-responders who lose < 2.0% of initial weight during a 4-week BT run-in. Percent weight loss from randomization to week 24 is the study's primary endpoint.

2.4 Secondary Objectives of Phase 2

- To compare early non-responders treated with BT+M and BT+P on weight loss in kg from randomization to week 24.

- To compare the portion of early non-responders who achieve a post-randomization loss of ≥ 5% and ≥ 10% of initial body weight with BT+M and BT+P.

- To compare non-responders treated with BT+M vs. BT+P in changes in hunger, satiety, relative reinforcing efficacy of food, and impulsivity between randomization and week 24.

- To explore differences in percent weight loss from randomization to week 24 between early non-responders treated with BT+M and early responders treated with BT alone.

3 Investigational Plan

3.1 General Design

This is a two-phase study. Phase 1 will evaluate obesity-related behavioral and biological characteristics as potential mechanisms of non-response to BT. Phase 2 is a double-blind, placebo-controlled, RCT to test whether augmenting BT with weight loss medication improves 24-week weight loss, as compared to BT with placebo, in subjects identified as early non-responders to 4 weeks of individual behavioral weight control. Subjects will be a total of 150 adults, aged 21-70 years, with a body mass index (BMI) of 31 kg/m^2 or above (28 kg/m^2 with an obesity-related comorbidity). Subjects will attend a screening visit in which they will complete a behavioral evaluation with a psychologist and a medical history. In phase 1, eligible subjects will complete questionnaires and an in-person baseline assessment of obesity-related behavioral characteristics (satiety, hunger, RRV_{food}, and impulsivity), neuropeptides, and gastric emptying. Within 2 weeks of this assessment, they will begin an initial 4-week BT "run-in" delivered individually in 20-30 minute sessions. The primary goal of phase 1 will be to evaluate baseline postprandial satiety, postprandial change in GLP-1, and gastric emptying as predictors of early weight loss after 4 weeks of BT. We will also examine whether these variables predict categorization as an early non-responder to BT who loses < 2.0% of initial weight (vs. early responders who lose ≥ 2.0%; approximately 33% vs. 66% of the sample, respectively).

In phase 2, early non-responders (who lost < 2.0% during the BT run-in) will be randomly assigned to 24 weeks of: 1) BT plus placebo (BT+P); or 2) BT plus medication (BT+M; phentermine 15.0 mg). Both treatment groups will continue to attend 20-30 minute individual BT sessions, weekly for the first 12 weeks and every other week for the last 12 weeks (total of 18 visits). Both treatment groups will also take once daily study medication (placebo or phentermine 15.0 mg) for the duration of the intervention period (with titration between randomization and week 2). Early BT responders identified during the run-in will receive the same 24-week BT program, but will not receive study medication or be included in the randomized trial. The assessments administered at baseline – questionnaires, including behavioral testing, blood draws, and measurements of body weight – will be repeated at randomization (week 0) and at week 24.

Comment. The use in phase 2 of an adaptive design, in which hypotheses only include participants who do not lose ≥ 2% with 4 weeks of BT, minimizes the size of the randomized sample treated in the current study. However, the initial sample size of 150 participants needed to assess weight loss predictors and identify at least 50 early non-responders is large for a K23 award. To limit treatment burden, we considered offering early responders no further treatment or a less intensive intervention following the 4-week diet run-in. However, we thought that offering responders a low-intensity treatment (or no treatment), which is known to produce suboptimal weight loss,[1] would not be ethical, and that doing so also would likely de-incentivize success during the 4-week run-in. We therefore decided to offer the same 24-week BT program to all participants who complete the run-in, regardless of responder status. Continuing to treat responders also allows us to conduct an exploratory analysis comparing the weight losses of these individuals to non-responders treated with BT + M. We also considered enrolling both early non-responders and early responders in the RCT. However, in consultation with program officers at NIDDK, we ultimately decided that it would be inappropriate to expose individuals to drug who were already successful with BT alone. Although we believe that the selected design provides the best balance between maintaining focus on the study's primary aim of improving treatment for early non-responders and the ethical care of all enrolled participants, the ongoing treatment of responders with BT limits our ability to recruit a larger initial sample with the aim of powering the study with enough non-responders to test secondary aims.

3.2 Allocation to Interventional Group

After completing 4 weeks of BT, subjects will attend a randomization visit (described to subjects as a "progress assessment visit") at which their weight will be measured, and they will be categorized as an early non-responder (loss of < 2.0% of initial weight) or early responder (loss of ≥ 2.0%). After early non-responders' eligibility is confirmed via a medical assessment, they will be randomly assigned in a 1:1 ratio, in randomly permuted blocks of 2 to 4 subjects, to one of the two treatment conditions. To maintain investigator blinding, randomization will be carried out by Penn's Investigational Drug Services who will

purchase phentermine and package the study medications (phentermine or placebo) in blinded capsules. The first subject to meet the randomization criteria will be assigned the first number in the sequence; each subsequent subject to meet randomization criteria will be assigned the next number in the sequence.

3.3 Study Endpoints

3.3.1 Primary Study Endpoints

The primary endpoints of phase 1 are percent weight loss from the start of the BT run-in (week -4) to randomization (week 0), as well as categorization as an early non-responder who lost < 2.0% of initial weight at randomization (co-primary outcomes), as predicted by postprandial satiety ratings (measured by visual analogue scales (VAS) during a test meal), postprandial change in GLP-1, and gastric emptying (measured using an acetaminophen test) at baseline.

The primary endpoint of phase 2 is change in body weight (i.e., % reduction in initial weight), as measured from randomization to week 24.

3.3.2 Secondary Study Endpoints

Secondary endpoints of phase 1 are percent weight loss from the start of the BT run-in (week -4) to randomization (week 0) and categorization as an early non-responder who lost < 2.0% of initial weight at randomization, as predicted by additional behavioral characteristics (hunger as measured by VAS ratings, RRV_{food} as measured using a computer task, and impulsivity as measured using a delay discounting computer task) and neuropeptides (higher fasting ghrelin, lower fasting leptin, and lower postprandial changes in insulin and PYY).

Secondary endpoints of phase 2 will include change in body weight in kg from randomization to week 24, as well as the portion of early non-responders who achieve a post-randomization loss of $\geq$ 5% and $\geq$ 10% of initial body weight. We will also examine differences between non-responders treated with BT+M vs. BT+P in changes in hunger, satiety, the reinforcing efficacy of food, and impulsivity (measured as described above) between randomization and week 24. The groups also will be compared on changes in past week VAS ratings of hunger, fullness, food preoccupation, food liking, and cravings as measured at treatment visits. A comparison will also be made in percent weight loss from randomization to week 24 between early non-responders treated with BT+M and early responders treated with BT alone.

3.3.3 Exploratory Endpoints

An exploratory analysis will compare the two randomized groups (BT+M vs. BT+P) on changes from randomization to week 24 in CVD risk factors (i.e., blood pressure, triglycerides, LDL and HDL cholesterol, and waist circumference), glycemic control (i.e., fasting blood sugar), quality of life (as measured by the Short Form Health Survey (SF-36), mood (as measured by the Patient Health Questionnaire (PHQ-9)), and physical activity (Paffenbarger Physical Activity Questionnaire).

An exploratory factor analysis will be used to determine whether primary and secondary predictor variables cluster into phenotypes. Exploratory endpoints will also include additional potential predictors of early response to BT. These will include measures of hunger (i.e., Eating Inventory [EI], past-week visual analogue scale [VAS] ratings), RRV_{food} (i.e., Power of Food Scale [PFS]), the reinforcing efficacy of food, general sensitivity to reward (i.e., the Behavioral Inhibition/Activation Scale [BIS/BAS]), impulsivity (i.e., the Barratt Impulsiveness Scale [BIS-15]), appetite (past-week VAS ratings), cognitive restraint (EI), disinhibition (EI), binge eating (i.e. the Questionnaire on Eating and Weight Patterns [QEWP-5]), food craving (i.e., Food Craving Questionnaire – Trait – reduced [FCQ-Tr]), emotional eating (Dutch Eating Behaviour Questionnaire [DEBQ]), perceived barriers to healthy eating and physical activity, diet and exercise self-efficacy (i.e., Weight Efficacy Life-Style Questionnaire [WEL], SCI Exercise Self Efficacy Scale [ESES]), social support for healthy eating and physical activity (i.e., Ball and Crawford Social Support Scale), hours of sleep per week, mindfulness and acceptance (Philadelphia Mindfulness Questionnaire [PHLMS]), food addiction (Yale Food Addiction Scale [YFAS]), indicators of withdrawal (Highly Processed Food Withdrawal Scale [ProWS]), perceived stress (i.e., Perceived Stress Scale), anxiety (i.e., GAD-7), and mood (i.e., PHQ-9).

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

1. BMI ≥ 31 kg/m² (or 28 kg/m^2 with obesity-related comorbidity)
2. Age ≥ 18 years and ≤ 70 years
3. Eligible female patients will be:
   - non-pregnant, evidenced by a negative urine pregnancy test
   - non-lactating
   - surgically sterile or postmenopausal, or they will agree to continue to use an accepted method of birth control during the study. Acceptable methods of birth control are: hormonal contraceptives; double barrier method (condom with spermicide or diaphragm with spermicide); intrauterine device; surgical sterility; abstinence; and/or postmenopausal status (defined as at least 2 years without menses).
4. Subjects must:
   - have a primary care provider (PCP) who is responsible for providing routine care
   - understand and be willing to comply with all study-related procedures and agree to participate in the study by giving written informed consent
   - plan to remain in the Philadelphia area for the next 9 months or more

4.2 Exclusion Criteria

1. Pregnant or nursing, or plans to become pregnant in the next 9 months.
2. Uncontrolled hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg)
3. Type 1 diabetes
4. Type 2 diabetes
5. A fasting blood glucose >126 mg/dL (on second assessment after first elevated value, patients are excluded if they have both fasting blood glucose > 126 mg/dL and HbA1c ≥ 6.5)
6. History of cardiovascular disease (e.g., coronary artery disease, stroke, arrhythmias, congestive heart failure, or heart block greater than first degree)
7. Clinically significant hepatic or renal disease
8. Hyperthyroidism
9. Other thyroid disease, not controlled.
10. History of malignancy (except for non-melanoma skin cancer) in past 5 years
11. Narrow angle glaucoma
12. Presence or history of marked agitation
13. Current severe major depressive episode (BDI-II score ≥ 29), current active suicidal ideation, or history of suicide attempts within the past 5 years.
14. Any severity of thought or bipolar disorder, or bulimia nervosa.
15. Psychiatric hospitalization within the past 6 months
16. Self-reported alcohol or substance abuse within the past 6 months, including at-risk drinking (current consumption of ≥ 14 alcoholic drinks per week)
17. Past year history of drug abuse.
18. Use in the past 2 weeks of monoamine oxidase inhibitors.
19. Current use of serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, duloxetine, desvenlafaxine, milnacipran, levomilnacipran).
20. Use in past 6 months of medications known to induce significant weight loss (i.e., prescription weight loss medications) or weight gain (e.g., chronic use of oral steroids, second generation antipsychotics)
21. Loss of ≥ 5% of initial body weight within the past 6 months
22. History of (or plans for) bariatric surgery (e.g., roux en y gastric bypass, sleeve gastrectomy, gastric banding), endoscopic intragastric balloon, or aspire assist.

23. Inability to walk 5 blocks comfortably or engage in some other form of aerobic activity (e.g., swimming)
24. Known or suspected allergy to sympathomimetic amines or related products
25. The receipt of any investigational drug within 6 months prior to this trial
26. Previous participation in this trial (e.g., randomized and failed to participate)
27. Changes to any chronic medication (type or dosage) within the past 3 months.
28. Any serious or unstable medical or psychological condition that, in the opinion of the investigator, would compromise the patient's safety or successful participation in the study

Other Therapy: Subjects will be expected to use medications (prescribed by their PCP) to control traditional cardiometabolic risk factors (e.g., hypertension, hypercholesterolemia, etc) and other co-morbid conditions, with the exception of medications listed above under "exclusions." In all cases, the subjects' PCP will be asked at the study's outset to keep medication does constant throughout the study, whenever possible. Subjects will be expected to have been on their medication regimen (including the dose) for 3 months prior to beginning the BT program.

4.3 Randomization Criteria

To be eligible to participate in the randomized phase of the trial, subjects must also:

1. Complete at least 3 out of 4 treatment sessions during the 4-week BT run-in and attend a randomization visit. Attending an in-person makeup session within one week of a missed visit will count as having attended the run-in visit.
2. Lose < 2.0% of initial weight during the 4-week BT run-in.

Subjects who complete at least 3 out of 4 treatment sessions during the 4-week BT run-in and have lost ≥ 2% of initial weight at the randomization visit will be provided with 24 weeks of BT during phase 2 of the study, but will not be eligible for randomization to a study medication.

4.4 Subject Recruitment

Subjects will be recruited from the greater Philadelphia area via flyers and online, radio, and print advertisements, through referrals from Penn primary care practices, and through Penn's iConnect system. All recruiting materials used in the study will have IRB approval.

4.5 Duration of Study Participation

The total duration of the study subjects' participation is expected to be 8 months. This includes a screening visit, baseline visit, 28 total weeks of BT (4 weeks before and 24 weeks after the randomization visit), and a post-treatment assessment.

4.6 Total Number of Subjects and Sites

Recruitment will end when 150 subjects are enrolled. It is expected that approximately 50 of these subjects (33%) will become classified as early non-responders to BT and enrolled in the randomized trial.

4.7 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Interventions

5.1 BT Run-in

All subjects will complete an initial 4-week BT program in which they will attend weekly individual weight loss sessions of 20-30 minutes led by practitioners with training and experience in the delivery of BT (e.g., registered dietitians (RDs), NPs, psychologists). Subjects will be instructed to consume a self-selected diet of 1200-1500 kcal/day (for those who weigh < 250 lb) or 1500-1800 kcal/day (for those who weigh ≥ 250 lb) and be asked to begin to gradually increase their physical activity levels. Subjects will be counseled on how to consume a well-balanced diet and will be taught to use calorie counting and self-monitoring (e.g.,

Myfitnesspal, paper diaries) to meet their goals.

5.2 BT Intervention

Following randomization, all subjects will continue to attend individual (20-30 minute) BT sessions weekly for 12 weeks, then every other week until week 24 (total of 18 sessions). Subjects will be instructed to continue to follow their calorie goal and to engage in low-to-moderate intensity physical activity (e.g., walking), gradually building to a goal of ≥180 minutes per week (spread across 5 days) by week 24. They will be provided a curriculum on behavioral weight control, based on prior studies, [80, 81] that includes self-monitoring, stimulus control, goal-setting, problem-solving, cognitive restructuring, and relapse prevention. Subjects will continue to monitor their food intake, physical activity, and weight online (e.g., Myfitnesspal) unless they prefer paper diaries. Subjects who miss a treatment visit will be contacted by the research coordinator and invited to complete a make-up session with study staff.

Initially, BT sessions were primarily provided in-person (make-up sessions were conducted in person or by phone). Consistent with University policy, all BT sessions will be provided by telehealth (phone or secure teleconferencing system) while recommendations to maintain remote activities due to COVID-19 remain in place.

BT interventionists will include RDs, NPs, and psychologists who are experienced in delivering lifestyle modification. Before beginning the study, interventionists will receive a 2-hour overview of obesity and its behavioral management, followed by ongoing weekly group clinical supervision. The PI will observe each provider delivering a treatment session at least once every 6 months to provide individualized feedback and ensure protocol adherence.

5.3 Medication and Placebo Interventions

In addition to attending BT sessions, non-responders will take a once daily study medication (phentermine or placebo) beginning at the randomization visit. The study medication will be provided in capsule form, and participants will be encouraged to take the medication in the morning upon awakening. Subjects will receive a 30-day supply of the study medication on each of 6 occasions. Phentermine will be provided as 8.0mg/d for the first 2 weeks to facilitate its acceptance to participants. The dose will be increased at week 2 to 15 mg/d (or further placebo) in all participants. Phentermine (or placebo) will be down-titrated (back to 8.0mg/d) or terminated in patients who report that they cannot tolerate the medication after a prolonged effort to do so. Down-titration will be managed in a blinded manner by Penn's Investigational Drug Service (IDS), in response to notification from the principal investigator (or study co-investigators) of patients' complaints of symptoms. (With IDS, we successfully used this titration method in prior randomized placebo-controlled trials of sibutramine for weight loss [82] and of the addition for 12 weeks of phentermine or placebo to liraglutide 3.0 mg. [83]) Participants in whom phentermine (or placebo) is terminated will continue to receive BT for the remainder of the 24-week treatment period.

5.4 Preparation and Packaging of Study Medications

Phentermine (and placebo) will be purchased and then packaged in blinded capsules by Penn's Investigational Drug Service (IDS). IDS has prepared medications before for our Center in this manner, including the preparation of phentermine and placebo for a recent 12-week trial. [83] IDS will store all phentermine-placebo at the hospital, to be picked up on a weekly or every-other-week basis by study coordinators and distributed to study patients.

5.5 Medication Storage

Drug supplies will be kept in a secured enclosure with limited access, both at the IDS where the medication is packaged, and at the Center for Weight and Eating Disorders (the Center), where it will be dispensed to subjects. The PI and research coordinator will ensure the availability of proper storage conditions at the Center. We will maintain adequate drug inventory and security at all times. Unused medication(s) will be stored separately from used trial medication(s). The PI will take appropriate precautions to prevent theft or diversion of the study drug.

5.6 Blinding

A master file of subject assignments will be kept by the pharmacists at IDS. Once a subject is randomized, the research team will receive a medication blister pack or container labeled with the subject identification number from IDS. The research team and the subject will be blinded and will not know the investigational product contained in the container. The blind may be broken in the case of an emergency. To request unblinding, the PI or a member of the study team who has been authorized by the PI will contact IDS to receive the relevant subject(s)' information.

5.7 Administration and Accountability

A record of product administration will be maintained by IDS and in the subject's file by the study team, including the medication identification number, date of distribution, and date that the product was returned by the subject. A standard form will be utilized to document this information throughout the study period.

5.8 Subject Compliance Monitoring

BT interventionists will briefly review the subject's medication adherence at each visit, determining the number of days the medication was used each week and identifying reasons for missed doses. The number of doses of medication taken each week will be tracked. Interventionists will help subjects to problem solve barriers to adherence to the medication regimen and will refer subjects to the study physician or NP on an as needed basis. Subjects will be asked to return used medication containers, which will allow the study team to obtain an objective measure of the subject's adherence to the medication regimen.

6 Study Procedures

Table 1. Proposed timeline of study visits and procedures for non-responders who lose < 2% and responders who lose ≥ 2% of initial weight after 4 weeks of intensive behavioral treatment (BT).

	Screening	Baseline and Start of IBT Run-in	Non-randomized IBT Run-in			Randomization	Randomized Treatment																	Post-Treatment
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Weeks in relation to randomization	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24
Treatment																								
Non-responders who lose < 2% at week 4																								
BT session			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phentermine or placebo						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication distribution: 8.0 mg						X																		
Medication distribution: 15.0 mg								X		X				X				X		X		X		
Responders who lose ≥ 2% at week 4																								
BT session			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment																								
Informed consent	X																							
Behavioral assessment	X																							
Medical history	X																							
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMP, lipids	X					X																		X
Urine pregnancy test (for women of child-bearing potential)	X					X																		
Neuropeptides (GLP-1, insulin, PYY, leptin, ghrelin)		X				X																		X

Acetaminophen test (blood draw at 30 minutes after standard preload)		X				X																	X
Behavioral testing (progressive ratio task, delay discounting)		X				X																	X
Weekly VAS appetite rating		X	X	X	X	X	X	X	X	X		X		X		X		X		X	X	X	X
Questionnaires		X				X																	X
Safety																							
Vital signs measurement	X	X				X	X	X	X	X		X		X		X		X		X		X	X
Brief medical visit – non-responders						X		X		X													X

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7.1 Screening Procedures

Phone screens will be conducted by trained staff to assess preliminary eligibility. Individuals who appear to be eligible will be invited for an in-person screening visit that will include a behavioral evaluation conducted by a psychologist (including the PI). Prior to their screening visit, applicants will complete questionnaires that are administered as part of standard clinical practice at the Center for Weight and Eating Disorders: the Beck Depression Inventory-II (BDI-II) [84] to assess symptoms of depression; and the Weight and Lifestyle Inventory (WALI) [85] to provide information about the individual's weight history, disordered eating behaviors, and other health behaviors (e.g., food intake, alcohol consumption).

The in-person interview will be conducted by a psychologist, who will obtain informed consent and evaluate subjects' behavioral eligibility (i.e., willingness and appropriateness to participate). This will include our assessment of the applicant's mood (as measured by interview and the BDI-II) and suicidality (including history of suicidal ideation and behavior, as assessed at screening by interview and the Columbia-Suicide Severity Rating Scale [86]). Subjects who remain interested and pass this portion of the assessment will provide a medical history and physical examination to determine medical eligibility. Persons who continue to remain eligible will proceed to have a fasting blood test to determine that final eligibility criteria are met. Safety screening labs will include a comprehensive metabolic panel (CMP) and lipid panel, and a urine pregnancy test (for females of child-bearing age). An electrocardiogram (EKG) also will be performed to confirm medical eligibility prior to any participant's enrollment in the randomized trial. We anticipate completing 180 in-person screenings to obtain an initial sample of 150 subjects.

7.2 Randomization Visit

Following the 4-week BT run-in, subjects will attend a randomization visit (week 0, described to subjects as a "progress assessment visit") at which their percent weight loss from the start of the BT program (week -4) will be calculated. Subjects who have lost ≥2% of initial weight at this time will be categorized as early responders and will not be eligible for participation in the randomized trial. These subjects will be offered an additional 24 weeks of BT but will not receive a study medication.

Subjects who have lost <2% of initial weight at the randomization visit will be categorized as early non-responders. Trained research staff will review with randomization-eligible subjects information related to the study medication, including possible risks and benefits, and will confirm applicants' willingness to participate prior to enrolling them in the randomized phase of the trial. Interested subjects will then have their eligibility confirmed by trained research staff, including completion of a urine pregnancy test. Non-responders who remain eligible will be randomly assigned in double blinded fashion in a 1:1 ratio to receive either phentermine 15.0 mg or placebo, combined with an additional 24 weeks of BT. They will then meet with trained research staff who will instruct them in the use of the study medication and provide the first month's supply of medication.

All subjects will then complete an outcome assessment, as described below.

7.3 Outcome Assessments

All subjects will be asked to attend 3 outcome assessments, which will occur at baseline (week -5,), randomization (week 0) and week 24. These assessments will include an evaluation of potential predictors of weight loss and assessment of the primary outcome measures used to judge the effectiveness of the treatments in inducing weight loss (described below). BT responders (who do not participate in the randomized trial) will provide weight, CVD, and questionnaire outcome measures at week 24, but will not be asked to complete the other portions of the in-person assessment at that time.

Each in-person outcome assessment visit will take approximately 2 hours. Subjects will be asked to fast for 8 hours prior to the in-person visit (overnight fast). Questionnaire measures will be completed online within 2 weeks of the in-person visit. A paper version of these measures will be provided to subjects upon request.

7.4 Treatment Visits

As described above, subjects will attend 4 initial, once weekly, 20-30 minute, individual BT sessions ("BT run-in;" week -4 to week -1). The first BT session will be scheduled immediately following the baseline outcome assessment. After completing the randomization visit (week 0), all subjects will continue to attend

BT sessions, provided in the same treatment format, weekly for the first 12 weeks (12 sessions) and every-other-week for the last 12 weeks (6 sessions).

7.5 Missed Visits

Subjects who miss a treatment visit will be contacted by the research coordinator and invited to complete a make-up session with study staff, in person or by phone (except for visits at which medication is distributed). Subjects who do not attend a randomization visit within 2 weeks of the end of the BT run-in will not be eligible to continue participation in the study. All subjects who complete a randomization visit will be invited to complete the week 24 assessment, even if they have discontinued the study medication or attendance of BT visits.

7.6 Subject Withdrawal

A subject may voluntarily withdraw from the study at any time for any reason. The investigator or sponsor also may withdraw the subject from further participation at any time, if it is considered in the best interest of the subject or the study, without prejudice to the subject's future medical care. It will be documented whether or not each subject completes the clinical study.

The primary reason for a subject's premature discontinuation from the study will be selected from the following standard categories and documented in the source documents:

Adverse event (AE): One or more clinical or laboratory events which, in the medical judgment of the investigator, are grounds for discontinuation, even if the event does not appear to be related to study drug. The subject may withdraw because of an AE even if the investigator does not feel that it is grounds for discontinuation. This category includes subject death.

Withdrawal of consent: The subject desires to withdraw from further participation in the study.

Lost to follow-up: In the case of subjects who do not return to the center for study procedures and cannot be contacted, study personnel will make vigorous and repeated attempts (minimum of 3) to contact the subject. If all attempts to contact the subject fail, that subject will be considered to be lost to follow-up and discontinued from the study.

Protocol violation: The subject's laboratory or other findings or conduct fail to meet the protocol entry criteria or fail to adhere to the protocol requirements.

Subject pregnancy or intention of becoming pregnant

The **Stopping Criteria** for individual subjects include:

1. The Principal Investigator and/or Medical Monitor conclude it is unsafe for the subject to continue.
2. A new diagnosis is made of a significant medical condition which could influence the response to phentermine (e.g., congestive heart failure).
3. A medication is begun that could alter the subject's responses to phentermine.

Subjects meeting individual stopping criteria will be withdrawn from the trial.

7.7 Early Termination Visits

Whenever possible, subjects who withdraw early or who are asked by the investigator to cease participation in the study will have one final visit to collect study medication and to follow up regarding adverse events.

8 Study Evaluations and Measurements

The following measures will be collected during all outcome assessments, unless otherwise specified.

8.1 Primary Outcome Measure: Body Weight

Body weight will be measured at screening and at all clinic visits. However, for purposes of the primary outcome, weight will be assessed during outcome assessments at baseline (at the start of the BT run-in); at randomization (week 0); and at week 24. Weight will be measured on a digital scale (to the nearest 0.1 kg) with subjects dressed in light clothing, without shoes. Two measurements will be taken on each occasion.

8.2 Phase 1 Predictor Variables

8.2.1 Appetite, Neuropeptides, and Gastric Emptying

During the two-hour in-person outcome assessment at baseline (week -5), randomization (week 0) and week 24, subjects will first complete measures of appetite, neuropeptides, and gastric emptying before and for 60 minutes after consumption of a liquid test meal (e.g., Muscle Milk). The test meal size (oz and kcal will vary by sex with women consuming 70% of the amount provided to men. Subjects will be asked to fast for 8 hours prior to the in-person assessment (overnight fast), and research staff will confirm the timing of the subject's last ingestion prior to beginning the assessment.

Appetite measures are perceived ratings of hunger, fullness, and satiety that reflect both objective (e.g., physiological) and subjective (e.g., learned) components of appetite. They will be assessed using 100-mm visual analog scales (VAS) with opposing anchors (e.g., "extremely full" to "not at all full"). [16, 17] The satiety quotient (SQ) will be the primary measure of perceived satiety and reflects the extent to which the liquid test meal reduces appetite sensations per unit of intake (e.g., kcal), [16, 17] calculated as: SQ (mm/kcal) = [(fasting rating before preload – 60 min post-preload rating)] / (energy content of preload) x 100. Physiological appetitive response will be measured as: 1) fasting levels of circulating neuropeptides associated with appetite (GLP-1, insulin, PYY, leptin, and ghrelin); 2) postprandial changes in these neuropeptides, calculated as the 60-minute area under the curve (AUC); [45] and 3) gastric emptying as assessed by an acetaminophen test (60-minute AUC).[87-89] Because acetaminophen is minimally absorbed by the stomach but quickly enters the bloodstream in the small intestine, gastric emptying is considered to be the primary factor influencing its appearance in the blood. [87-89] Maximum blood concentration of acetaminophen is reached in 30 to 60 minutes; therefore, the 60-minute AUC is thought to represent rapidity of gastric emptying.[89]

Blood samples and VAS scales will first be completed in a fasted state. Subjects will be given 1.5g of acetaminophen with 50 ml of water. [87-89] They will then be asked to consume a liquid test meal within a 10-minute period. Subjects will repeat VAS ratings at 10-minute intervals after consumption of the test meal.[27] Postprandial blood samples will be collected at 30- and 60-minutes post-ingestion to evaluate changes in circulating neuropeptides and acetaminophen absorption. Protease inhibitors and DPP4 inhibitors will be added to samples to be assayed for GLP-1, PYY, and ghrelin to prevent enzymatic breakdown. Samples will be centrifuged at 4°C, separated, and frozen at −80°C for later analysis.

8.2.2 Impulsivity

After completion of the final blood draw and appetite ratings, subjects will complete measures of impulsivity (delay discounting; DD), reinforcing efficacy (questionnaire), and the relative reinforcing value of food (RRV_{food}; baseline [week -5] only). The completion of these tasks following consumption of the liquid meal is designed to reduce the effect of hunger on food reinforcement. [e.g., 33]

DD is conceptualized as an aspect of impulsivity that reflects difficulty with inhibiting responses to rewarding stimuli. The measure indicates the degree to which delaying an outcome reduces its perceived value. DD will be assessed via a computer program in which subjects are offered choices between small, immediate rewards and larger, delayed rewards. [e.g., 28, 32] The size of the larger amount is fixed, while the size of the smaller reward and length of delay vary between trials. Indifference points are calculated as the point at which the subject switches preference from the immediate to the delayed reward, and the AUC (representing the ratio of immediate reward size to time delay) will be used as the primary outcome.[28, 32]

8.2.3 Relative Reinforcing Value of Food

RRV_{food} refers to how hard a person is willing to work to gain access to a food reinforcer. Subjects are allowed to work to earn points from a slot machine task at either of two computer stations, one of which

provides points towards obtaining a preferred high-calorie food, and the other points towards a preferred low-calorie food. [e.g., 29, 30] Points are earned on a progressive ratio scale that increases at fixed intervals. The primary outcome is the number of food reinforcer points earned, which is thought to reflect the subject's willingness to allocate time and effort to obtaining desired foods.

8.3 Cardiometabolic Risk

To evaluate exploratory outcomes, cardiometabolic risk factors will be assessed at screening, randomization (week 0) and week 24. Fasting blood samples (i.e., following an overnight fast of at least 8 hours) will be drawn on each occasion and assayed for a CMP and lipid panel. (Samples will be analyzed by Quest Diagnostics.) Responders who are not randomized will not complete the CMP and lipid panel at randomization (week 0). All participants will complete these analyses at screening and at week 24.

Blood pressure and pulse will be measured on each occasion using an automated monitor (Dinamap, model 9300). Two readings will be taken on each occasion (at 1-minute intervals), after subjects have been seated for at least 5 minutes. Waist circumference (measured horizontally halfway between the lowest rib and the top of the hipbone) to the nearest 0.1 cm will be assessed on the same schedule. Two waist measurements will be obtained at each assessment visit.

8.4 Questionnaire Measures

Eating characteristics. Self-report measures of hunger, impulsivity, and the relative reinforcing value of food will be administered to all subjects at all three outcome assessments. The Eating Inventory (EI – hunger subscale [90]) and one-week VAS ratings will be used to assess hunger. RRV_{food} will be assessed by the Power of Food Scale (PFS [91]) and general sensitivity to reward will be assessed by the Behavioral Inhibition/Activation Scale (BIS/BAS).[92] The Barratt Impulsiveness Scale (BIS-15)[93] will be used to assess impulsivity. We will also collect measures of additional eating characteristics for use in exploratory analyses, including past-week VAS appetite ratings [94], cognitive restraint (EI), disinhibition (EI), and binge eating (Questionnaire on Eating and Weight Patterns [QEWP-5][95]). Craving frequency will be assessed using the Food Craving Questionnaire – Trait – reduced (FCQ-Tr)[96] and emotional eating using the Dutch Eating Behavior Questionnaire (DEBQ)[97] Emotional Eating subscale. Perceived barriers to health behavior change [98], diet and exercise self-efficacy (i.e., Weight Efficacy Life-Style Questionnaire [WEL][99], SCI Exercise Self Efficacy Scale [ESES][100]), social support for healthy eating and physical activity (i.e., Ball and Crawford Social Support Scale)[101], will also be assessed. Reinforcing efficacy of high- and low-energy density snack foods and active and non-active activities will be assessed using a computerized questionnaire during the in-person assessment.[114] Food addiction will be assessed using the Yale Food Addiction Scale (YFAS).[115]

The Highly Processed Food Withdrawal Scale (ProWS)[116] will be administered on a separate timeline from the questionnaires described above. Participants will first complete the ProWS at their screening visit (week -5) and will be sent an email every other day with a link to complete this questionnaire until the second intervention visit (week -2). This timeline will allow us to assess indicators of withdrawal that may develop early in treatment when an individual attempts to cut down on highly processed foods.

Psychosocial characteristics. Psychosocial characteristics will be assessed on the same schedule as the primary outcomes. Mood will be assessed using the PHQ-9[102] and the C-SSRS[86]. Perceived stress will be assessed using the Perceived Stress Scale (PSS)[103] and anxiety using the GAD-7. Quality of life will be assessed using SF-36.[104] The Philadelphia Mindfulness Scale (PHLMS) will be used to assess general mindfulness and acceptance.[117] Physical activity will be assessed by the Paffenbarger Physical Activity Survey.[105] A brief questionnaire will assess hours of sleep per week.[118]

9 Statistical Plan

9.1 Sample Size and Power Determination

A total sample size of 150 subjects will provide at least 80% power to detect all three primary outcomes. All power analyses were conducted using G*Power 3.1 at an alpha of .05. A correction for multiple comparisons is not proposed due to the preliminary nature of this research.

Phase 1: For the co-primary outcome - percent weight loss at the end of the BT run-in as predicted by baseline satiety, postprandial GLP-1, and gastric emptying - an estimated effect size for each predictor of

f^2 = .042 was selected as the lower estimate from studies predicting weight loss from VAS satiety ratings and GLP-1 (*r*'s ≥ .20).).[16, 106] (We did not find studies using gastric emptying to predict weight loss, and the effect sizes for comparisons between BMI categories of f^2 = .07 - .30 were less conservative.[43, 78]) Based on this estimate, a sample size of 150 subjects would yield 80% power to detect statistical significance for the three individual predictor variables. The second co-primary outcome - non-responder status as predicted by these three predictors in discriminant analysis - would have 90.1% power with this sample size, based on power analysis for a 2-group MANOVA for 3 response variables[107, 108] with an estimated combined effect size of f^2 = .10.

Phase 2: For the primary outcome - percent weight change from randomization to week 24 among early non-responders - estimated group means, variances, and attrition rates were derived from data from prior studies conducted at our Center and from previous research in early non-response to BT [e.g., 4]. The estimated treatment effect is based on the placebo-subtracted effect of 28 weeks of phentermine 15.0 mg of 4.5 kg (4.4% of initial weight), as determined by a multi-arm RCT that enrolled 219 total patients in the placebo and phentermine 15.0 mg groups. [77] We selected this result as the basis of our power analysis because it most closely matched the phentermine dose and duration used in the present study. Other previous RCTs examining the effect of phentermine monotherapy have typically administered a 30.0 mg dose for 12 to 16 weeks. The majority of these trials have achieved larger placebo-subtracted weight losses of 5.4 to 7.8 kg. [72, 74-76] (One randomized trial reported a 4.0 kg placebo-subtracted loss with a different formulation, phentermine resin 30.0 mg, [73] and one reported a 3.3% placebo-subtracted loss when both phentermine 37.5 mg and placebo were combined with a 900-1100 kcal/day meal replacement diet, resulting in large mean weight losses in both groups. [109]) An additional study suggested that the difference in mean weight loss between phentermine 15.0 mg and phentermine 30.0 mg (both when combined with lorcaserin) is small (0.6 kg mean difference). [110] We therefore believe that participants provided with 24 weeks of phentermine 15.0 mg are likely to achieve a placebo subtracted loss of ≥4.5% of initial weight. (Most early phentermine studies reported results in kg, which is roughly equivalent to percent weight loss in populations with obesity.)

We predict a 24-week post-randomization weight loss among early non-responders of 6.5% in BT+M and 2.0% in BT+P, with expected standard deviations of 5.5%. We expect 33% of the initial baseline sample of 150 subjects to be categorized as early non-responders following the BT run-in.[4, 7, 8] Based on these estimates, a randomized sample size of 50 non-responders (25 per group), assuming a 20% attrition rate, will give us 81.5% power to detect between-treatment group differences at week 24 of 4.5% (effect size: *d* = 0.82).

9.2 Statistical Methods

Data quality and integrity will be checked by assessing the data for missing and out-of-range values and univariate normality with basic statistical procedures, including descriptive statistics and visual graphical displays (e.g., histograms, scatter plots). All questions of data quality and integrity will be investigated before any statistical modeling is conducted. To test the adequacy of randomization, preliminary analyses will include a comparison of demographic and baseline characteristics between randomized treatment groups (BT+P and BT+M; t-tests or Wilcoxon rank sum tests for continuous variables and Chi-Square test or Fisher's Exact test for categorical data). If baseline imbalances are observed, the relevant variables will be included as covariates in analyses relevant to those outcomes.

All analyses will be conducted using the ITT principle. Analyses will be two-tailed with an alpha of 0.05, and will be conducted using SPSS version 24.0 or SAS version 9.4. For all analyses, residual analyses will be conducted to check for outliers, influential points, and violations in the normality assumption. If violations are detected, variance-stabilizing transformations will be considered.

Phase 1: Analyses will be based on the initial population of subjects who attend at least one post-baseline treatment visit during the BT run-in. Multiple regression will be used to evaluate predictors of early weight loss with BT (% loss at week 0) and discriminant analysis will be used to assess which variables predict categorization as a non-responder (who has lost < 2% of initial weight at week 0). The primary analyses will test the hypothesis that the set of baseline satiety measures (VAS satiety ratings, postprandial changes in GLP-1, and gastric emptying) predict these outcomes when considered simultaneously. Additional analyses will evaluate demographic characteristics, secondary predictor variables (fasting hunger, RRV_{food}, reinforcing efficacy of food, impulsivity, fasting ghrelin, fasting leptin, and lower postprandial changes in insulin and PYY), and exploratory variables as predictors of early weight loss.

Factor analysis will be used to assess whether predictor variables cluster into phenotypes.

Phase 2: Primary analyses will be based on the all-randomized population. The null hypothesis being tested is that there will be no significant difference between non-responders assigned to BT+M and BT+P in mean percentage of initial weight lost at 24 weeks post-randomization. To assess the primary phase 2 outcome of percent weight change by treatment group (among non-responders), a mixed effects model will be fit with treatment group (BT+P, BT+M) as a between-subjects factor and time (week) as a within-subjects factor. We will use the group x time interaction to estimate and test treatment group differences at week 24 (primary endpoint). In fitting the mixed effects model with residual maximum likelihood, a variance-covariance structure will be selected based on criteria such as the Akaike's Information Criterion (AIC). The results from the mixed model will be summarized by mean (SE) for each treatment group at week 24. Secondary analyses comparing IBT+M and IBT+P in changes in hunger, satiety, reinforcing efficacy of food, and impulsivity from randomization to week 24 will be conducted using similar analytic strategies, as will exploratory analyses of change in cardiometabolic risk factors, quality of life, and depression. Similar mixed effects models also will be used to compare differences in percent weight loss from randomization to week 24 between early non-responders treated with BT+M and early responders who attend a randomization visit and are treated with BT alone. Logistic regression will be used to examine differences between BT+M and BT+P in percent of subjects who achieve a post-randomization loss of $\geq$ 5% and $\geq$ 10% of initial body weight at week 24. Subjects who do not provide a week 24 weight will be considered as not having achieved the categorical weight loss.

9.2.1 **Missing Data**.

All analyses will be conducted using the ITT principle, in which all available data on all randomized patients are included. This approach minimizes bias if subjects drop out of the intervention for different reasons. Assuming adequate fit of the mixed effects models to the data, the proposed nested random effects models are the most robust to missing data assumptions among standard longitudinal models that analyze all subjects regardless of how many post-randomization visits are missed.[111] The following missing or unbalanced data scenarios can be accommodated by such models: attrition (drop out), missed interim visits, and missing covariate data where a subject is interviewed but data are missing on covariates of interest. All three types of missing data are handled by way of maximum likelihood under the proposed mixed effects models and the missing at random assumption (MAR). Therefore, we will explore the potential bias of missing data by comparing completers and non-completers to see if they differ systematically on values of non-missing variables. There are many ways to assess the assumption of MAR. We will consider imputing missing endpoint data using multiple imputation techniques, fitting selection models (e.g. MNAR), and fitting pattern mixture models. Sensitivity analyses, including an analysis of the protocol-compliant population, also will be conducted.

Participants' data will be excluded from analyses in the event of pregnancy, amputation, bariatric surgery, or death. Any data collected following such events will be treated as missing, using the analytic methods described above. Additional criteria associated with subject censorship will be considered prior to initiating recruitment.

9.3 Subject Population(s) for Analysis

- Initial population: Any subjects who complete a baseline assessment and attend at least one post-baseline treatment session during the BT run-in
- All-randomized population: Any subjects who lose < 2% of initial weight during the BT run-in, attend a randomization visit, and are randomized to participate in the 24-week RCT comparing BT+M to BT+P
- Protocol-compliant population: Any subject who was randomized and received the protocol required investigational product exposure and required protocol processing during the RCT

10 Safety and Adverse Events

10.1 Definitions

10.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study, whether or not considered drug related. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

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

10.1.2 Serious Adverse Event

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

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

The term life-threatening in the definition of SAE 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 was more severe.

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

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

10.2 Recording of Adverse Events

All events meeting the definition of an adverse event will be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the 24 week treatment period as stated in the protocol. At each contact with subjects, study personnel will be responsive to reports of AEs with specific questioning and, where appropriate, by physical examination. Information on all adverse events will be recorded immediately in the source document and reported immediately, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though should be grouped under one diagnosis.

All AEs occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

The study PI is ultimately responsible for the recording, and reporting, unanticipated problems related to the research, which occur during the study.

10.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be characterized by the PI in consultation with the study physician. The relationship of AEs to the study will be classified as follows:

- Probable: Good reasons and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event is most likely related to an etiology other than the trial product

10.4 Reporting of Adverse Events and Unanticipated Problems

The PI will report all adverse events including serious adverse events (SAEs, as defined above) to the Safety Monitoring Committee established for the trial, and to the Penn IRB. All serious adverse events will be reported to the IRB within 72 hours, as required.

If the SAE report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report will include:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally, all other events (unanticipated problems, adverse reactions, and subject complaints) will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual.

10.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The PI is responsible for ensuring that all SAE are followed until either resolved or stable.

10.4.2 Pregnancy

Study subjects will be instructed to notify the investigator immediately if they become pregnant. Reporting of pregnancy by the investigator will occur within the same timelines described above for reporting of Adverse Events. Pregnancy complications will be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this will be reported and followed up as a serious adverse event.

There is no documented risk for males who reproduce while taking phentermine. Reported pregnancy in a non-participating female partner of a study subject will not be considered an adverse event, and follow-up data will not be requested.

Randomized female participants who have received a study medication and have become pregnant during the trial period will be followed until the pregnancy outcome and the new-born infant is 1 month of age. "Pregnancy outcome" is defined as the end of pregnancy: live birth, fetal death, or termination of pregnancy. Data will be collected via the participant's self-report; we will also attempt to obtain medical records related to the pregnancy and the pregnancy outcome.

The following information will be collected from all participants at the time of the reported pregnancy:

- Date of investigator's first knowledge of the pregnancy
- Participant weight and height at the time of becoming pregnant

- Whether the participant was exposed to a study medication, including medication start date, stop date, and dose at the time of withdrawal from the study
- First day of last menstrual period
- Expected date of delivery (if known)
- Number of fetuses (if known)
- Relevant risk factors and diagnoses with an onset prior to the current pregnancy (e.g., parvovirus; inheritable disease; rubella; toxoplasmosis; type 1 or 2 diabetes mellitus; gestational diabetes mellitus; cytomegalovirus; heart disease; hypertension; congenital anomaly [in mother]; psychomotor retardation; psychiatric illness during pregnancy; chemotherapy; radiation therapy; teratogenic exposure; thyroid disease; seizure disease; hepatitis A, B, C, or D; rhesus [RH] negative; tobacco, alcohol, or substance use during pregnancy; consanguinity; other past/current diagnoses or factors which could affect pregnancy outcome)
- Relevant risk factors and diagnoses with an onset during the current pregnancy
- Any adverse events experienced in connection with the current pregnancy
- Any adverse events occurring in the fetus during the current pregnancy

The following information will be collected from all randomized participants after the pregnancy outcome:

- Date of pregnancy outcome
- Gestational age at time of pregnancy outcome
- Whether the pregnancy resulted in a live birth.
    - If yes: number of live births and whether infant(s) was/were diagnosed with congenital anomalies at birth.
- Whether the pregnancy resulted in fetal death.
    - If yes: number of fetal deaths, early (before 20 weeks gestation) or late (after 20 weeks gestation), and whether the fetal death(s) were due to congenital anomalies
- Whether the pregnancy was terminated
    - If yes: whether the pregnancy was terminated due to congenital anomalies
- Delivery information (if applicable): vaginal or cesarean section, whether complications occurred during delivery
- For each live birth:
    - Gender
    - Length and weight at delivery
    - Apgar score at 1, 5, and 10 minutes (if known)
    - Diagnosis of health problems at delivery
    - Diagnosis of health problems between birth and age 1 month
    - Was the newborn diagnosed with congenital anomalies

10.5 Unblinding Procedures

Breaking of the blinding code will occur at the request of the PI following completion of the week 24 assessment of the last enrolled subject.

The code for a particular subject may be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject or if demanded by the subject. Whenever a code is broken, the person breaking the code must record the time, date and reason as well as his/her initials in the source documents. All codes (whether broken or not) will be kept throughout the trial period. Accountability of all broken or unbroken codes (hard copy or electronic) will be performed at or after trial closure.

10.6 Medical Monitoring

Safety endpoints include physical examination, adverse events (AEs), and standard laboratory tests. In addition to assessment visits, randomized subjects will have a brief medical monitoring visit (10-15 minutes) with study staff (e.g., registered nurse) at week 2 (after 2 weeks at the 8.0 mg dose) and week 4 (after most subjects will have completed 2 weeks at the 15.0 mg dose) to monitor response to the medication. Study

subjects will be asked whether there has been any change in their health or medications. The study NP or physician will be available to assess the subject and evaluate and treat any adverse events.

Side effects will be queried during every study visit, and the study NP or physician will be available to assess the subject and evaluate and treat any adverse events. Subjects will be encouraged to contact study staff immediately should an AE occur between visits, and 24-hour contact information will be provided for study personnel and the study physician. If any AE requires treatment follow-up, subjects will be provided with appropriate referrals.

Subjects will have fasting blood draws (CMP and lipids) at screening, and at randomization (week 0; randomized subjects only) and week 24. Vital signs (blood pressure and pulse) will be measured at screening and any in-person visits occurring in weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24.

10.6.1 Data and Safety Monitoring Plan

Purpose. The data and safety monitoring plan is included to ensure the safety of subjects and verify the integrity of the data. This monitoring plan outlines the procedures for data verification and integrity, safety parameters, and monitoring and completion of regulatory documents.

Risk of Study. This study is anticipated to pose minimal risk. Intensive BT poses minimal risks and improves weight and health outcomes for the average subject. Phentermine 15.0 is an FDA-approved medication that has proven to be safe in persons with obesity and obesity-related comorbidities. Phentermine was approved by the Food and Drug Administration (FDA) in 1959 for "short-term" use, commonly interpreted as 12 or fewer weeks. The FDA had not yet begun to require long-term trials for obesity drugs at that time. [69] In 2012, the FDA approved the combination of phentermine (7.5 – 15.0 mg/d) plus topiramate for long-term weight management (e.g. ≥12 months). Phentermine (monotherapy) is the most widely used weight loss medication in the U.S. and is frequently prescribed in clinical practice for periods longer than 12 weeks. [69-71] A recent study of a large cohort of 13,972 individuals who had received phentermine found that risk of the composite outcome of a cardiovascular event or death was rare (0.3%) and that there was no increase in risk associated with a longer duration of phentermine use (up to 2 years). [69] The FDA did not require an Investigational New Drug (IND) application for the use of phentermine in the present study.

Who Will be Responsible for Monitoring? The PI (Dr. Tronieri) will be responsible for overseeing and monitoring the study. Safety and data quality monitoring will be performed on an ongoing basis by the PI and research coordinator, in consultation with Drs. Wadden and Berkowitz (study physician).

A Safety Monitoring Committee consisting of a safety officer and data officer will provide additional study oversight. This team will include at least one external (non-Center) reviewer. The Committee will be responsible for executing the data safety and monitoring plan, monitoring trial safety and efficacy, and complying with Public Health Service reporting requirements. This team will meet prior to the start of recruitment to review the protocol, human subjects' protections, and plans for data and safety monitoring. They will then meet at least twice per year to review the study's progress and de-identified group-level data for differential rates in adverse events (AEs) and key outcomes. The Committee will review adherence to the proposed rate of subject enrollment, inclusion/exclusion criteria, and diversity goals as outlined in this protocol.

How Will Monitoring be Performed? Safety and data quality monitoring will be performed on an ongoing basis by the PI and research coordinator, in consultation with co-investigators (including the study physician). The research coordinator will oversee the collection and entry of all study data. This includes ensuring that source documents exist for the data, that fields are completed appropriately, and that corrections are entered according to Good Clinical Practice guidelines. Any deviations from study procedures will be documented and reported to the Safety Monitoring Committee and the IRB.

Prior to conducing final data analyses, data will be checked for systematic errors and missing data, and a random subset of primary and secondary outcome data that has been entered manually will be checked against source documents to identify errors.

Study Initiation. The PI will be responsible for assuring that all staff and subjects understand and accept the obligations incurred in undertaking this study in accordance with all applicable regulations; the obligation to obtain informed consent; the obligation to obtain IRB review and approval of a clinical investigation before the investigation may be initiated and to ensure continuing review of the study by the IRB; and to keep the sponsor informed of such IRB approval and subsequent IRB actions concerning the study.

Ongoing Monitoring Meeting. Monitoring will be conducted in accordance with the Penn's Sponsor-Investigator Standard Operating Procedure. Monitoring meetings will be held regularly throughout the study. The first meeting will occur no later than two weeks after the first subject is enrolled. Subsequent monitoring will occur at weekly study meetings of research staff at the Center, including the PI and the study physician. At these meetings, the team will review subject accrual and retention, protocol compliance, reported side effects and AEs, and any other subject issues. The PI will meet semi-annually with the Safety Monitoring Committee.

Assessing Adverse Events. Monitoring for AEs will be conducted in real-time by all study personnel who have direct contact with subjects. Side effects will be queried during each study visit, and the study NP or physician will be available to assess the subject and evaluate (e.g., time of onset, nature of issue reported) and treat any potential AEs. Subjects will be instructed to contact study staff, including the study physician, if they experience any AE between study visits. The study physician or NP will determine the severity of the AE, its possible relation to phentermine treatment using standard criteria (not, possibly, probably, or definitely related), and the appropriate course of action for the study subject.

Reporting of Adverse Events. The PI will review all of the Adverse and Unexpected Event Case Report Forms, in collaboration with Drs. Wadden and Berkowitz. After removal of identifying patient information, all AEs will be reported to Penn's IRB and the Safety Monitoring Committee. Serious Adverse Events (SAEs) will be brought to the attention of the PI and study physician within 24 hours and to the attention of the IRB within 72 hours, as required. All adverse events and unanticipated problems (UPs) will be recorded, and a summary table will be presented to the IRB and DSMB annually.

Data, Safety and Monitoring Report. The PI will provide a summary of the data, safety, and monitoring report to the IRB and Safety Monitoring Committee on an annual basis. The report will include the subjects demographic characteristics, expected versus actual accrual rates, retention rates, any quality assurance or regulatory issues that occurred since the previous report, summaries of AEs, SAEs and UPs, and any actions or changes with respect to the protocol.

Evidence of Training in Human Subjects Research. All research personnel associated with this study will have completed Penn's CITI training for patient oriented research and HIPAA compliance training. Documentation of this training will be maintained in the study regulatory binder. The PI will directly supervise all members of the research team.

11 Study Administration, Data Handling and Record Keeping

11.1 Confidentiality

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

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

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

11.2 Data Collection and Management

The following data will be collected from subjects for research purposes: 1) questionnaires assessing demographic characteristics, weight loss history, health behaviors (e.g., eating habits and physical activity), quality of life, depression, hunger, satiety, the relative reinforcing value of food, and impulsivity; 2) medical history to evaluate exclusion criteria and cardiometabolic risk; 3) measurements of weight, height, waist circumference, and blood pressure; 4) blood samples sent to Quest Diagnostics to assess cardiometabolic risk factors; 5) blood samples sent to the Hayes laboratory or Translational Core laboratory at Penn to assess concentration of circulating neuropeptides; 6) urine samples for pregnancy testing; and 7) in-person

assessment of appetite before and after a liquid test-meal and behavioral assessments of delay discounting and the relative reinforcing value of food, collected via computer. Computer-based assessments of delay discounting and the relative reinforcing value of food will be collected in EPrime. Questionnaire data will be entered directly in RedCap by subjects (except for those requesting paper forms). Trained study personnel will enter other data from source documents into RedCap and a random subset of the primary and secondary outcome data that has been entered manually will be checked against source documents to identify errors.

All research personnel will complete Penn's Collaborative Institutional Training Initiative (CITI) Protection of Human Subjects Research Training and HIPAA Compliance Training. Study staff involved in handling biological samples will complete additional IRB training in bloodborne pathogens. Subjects will be assigned an ID that will be used in all study communications. Research datasets will include only subject IDs, with a separate, password-protected dataset linking names and ID numbers. Study information will be stored electronically in a password-protected drive or kept in locked files.

All applicable national and international guidelines, regulations, and Institutional Review Board (IRB) guidelines regarding subject privacy and confidentiality will be followed throughout the study. No identifying information will be included with stored research data, biological samples, clinical data, or reports of results. Penn network firewalls prevent unauthorized internal access to data, external access to data, and malicious intent to destroy data and systems. Controlled user access will ensure that only appropriate and authorized personnel are able to view, access, and modify study data. Data sent to the IRB, Investigational Drug Services, or the Safety Monitoring Committee will contain no identifying information, except as required when reporting AEs. Password-protected files linking subject names and ID numbers will only be accessible to the PI and research coordinator, and will be stored in a locked office.

11.3 Records Retention

We will retain all Essential Documents in accordance with Federal regulation and International Conference on Harmonization (ICH) Good Clinical Practice (E-6) and 45 Code of Regulations (CFR) part74.53, which requires awardees to retain records pertinent to an award for a period of three years from the date of submission of the final expenditure report.

12 Study Monitoring, Auditing, and Inspecting

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

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

13 Ethical Considerations

This protocol and any amendments will be submitted to the Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The principal investigator (PI) will initiate and enroll subjects only after receiving IRB approval of the protocol and the informed consent documents. All recruiting materials used in the study will have IRB approval. Progress reports regarding the study will be submitted to the IRB in accordance with institutional and regulatory guidelines.

The study will be performed in compliance with applicable US government regulations and with the FDA Code of Federal Regulations for Good Clinical Practice (GCP). These procedures ensure the protection of the rights and the integrity of the subjects, adequate and correct conduct of all study procedures, adequate data collection, adequate documentation, and adequate data verification.

Before being enrolled, subjects will be provided informed consent. The nature, scope, and possible consequences of the study will have been explained in a form understandable to them. A copy of the consent document will be given to the subject. The PI will retain the original signed consent document.

Subject confidentiality will be maintained throughout the study according to applicable guidelines, regulations and IRB requirements. All laboratory samples, study clinical data, and reports of results will de-identify individual subjects. Subjects will be identified by initials, date of birth, and subject number only for use in data collection. Published data will provide subject numbers only if needed for clarity of presentation (e.g., in individual event listings).

The study will be conducted in accordance with the Declaration of Helsinki. The study will be conducted in accordance with the ICH GCP guidelines. The sponsor-investigator will comply with all applicable regulatory and legal requirements, ICH GCP guidelines, and the Declaration of Helsinki in obtaining and documenting the informed consent.

13.1 Risks

Potential Risks of Weight Loss Intervention: Rapid weight loss (loss of > 3 lb. per week for 3 or more weeks) may increase the risk of gallstones. Symptoms of gallstones include abdominal pain, nausea, vomiting, fever, and chills. Rate of weight loss will be monitored in all subjects to identify those at risk.

Potential Risks of the Medication: The following are the common side effects that have been reported with phentermine treatment (because the medication was approved in 1959, they do not have a defined frequency): high blood pressure, palpitations, elevated heart rate (tachycardia), dizziness, overstimulation, restlessness, insomnia, changes in mood (euphoria or dysphoria), changes in libido, tremor, headache, dry mouth, unpleasant taste, diarrhea, constipation, and other gastrointestinal disturbances.

Rare side effects that may be associated with taking phentermine include:

- **Acquired Valvular Heart Disease.** Cases of developing heart valve disease were reported in people taking phentermine in combination with fenfluramine. Fenfluramine appeared to be responsible for the valvular heart disease. It was removed from the market in 1997. Phentermine did not appear to contribute to valvular heart disease, but this possibility cannot be completely ruled out.

- **Primary Pulmonary Hypertension. This condition is a rare, frequently deadly disease of the lungs. It was observed in persons who took the combination of phentermine and fenfluramine.** Fenfluramine appeared to be responsible for this illness and was removed from the market. The possibility of an association between primary pulmonary hypertension and the use of phentermine alone cannot be ruled out. No cases of the disease have been reported with the long-term use of phentermine and topiramate, marketed as Qsymia.

- **Abuse Potential**. Phentermine is chemically and pharmacologically similar to amphetamines which have a high abuse potential. One study found no signs of drug craving, abuse, dependence, or amphetamine-like withdrawal upon abruptly ceasing the medication, even at doses higher than typically recommended and after treatment durations of up to 21 years.[71] However, the possibility of abuse with phentermine should be considered in deciding whether to prescribe this medication. Individuals who have a history of drug abuse will not be eligible to participate.

- **Central Nervous System Effects.** Phentermine may impair physical and mental abilities. Caution should be taken when driving or operating machinery, or drinking alcohol. Individuals with an overactive thyroid (hyperthyroidism) will not be eligible for to take phentermine.

- **Glaucoma**. Phentermine may cause excessive dilation of the pupils which can worsen narrow angle glaucoma. Patients with a narrow angle glaucoma diagnosis will not be eligible to participate.

- **Drug Interactions**. Use of phentermine is contraindicated during or within 14 days following the administration of monoamine oxidase inhibitors (MAOIs) because of the risk of hypertensive crisis. The effect of co-administering phentermine with selective serotonin norepinephrine reuptake inhibitors (SNRIs) has not been investigated. Participants will be asked to inform the study physician or nurse practitioner immediately if they are prescribed one of these medications during the study period.

- **Kidney Impairment.** Phentermine has not been studied in persons with kidney impairment. Persons with clinically significant kidney disease are not eligible for this study.

- **High Blood Pressure.** Phentermine may cause an increase in blood pressure. Individuals with a blood pressure is ≥140/90 not be eligible to participate in this study. Individuals with a history of coronary heart disease, congestive heart failure, or other significant cardiovascular disease (see exclusions) also will not be eligible. We will monitor participants' blood pressure at every study visit.

- **Unforeseen risks.** Such risks include allergic reactions to medications. In addition, there may be other risks associated with phentermine that have not been identified. If additional risks are identified during the study, study subjects will be informed about these risks by the study team.

- **Reproductive risks.** The use of phentermine may pose risks to pregnancy and/or an unborn baby. Therefore, subjects are advised not to get pregnant while in the study. Women of child bearing potential will be required to follow a study-approved method of birth control while participating in the study. Adequate birth control in this study is the use of double barrier methods (condom with spermicide or diaphragm with spermicide), stable hormonal contraception, intrauterine device, abstinence, or tubal ligation. In addition, the study medication may have unknown risks to breast-fed babies. Therefore, study subjects are instructed not to breastfeed while taking the study drug.

Risks of the Assessment: Risks of drawing blood include pain, bruising at the puncture site, swelling, feeling faint or lightheaded, and, rarely, infection.

Confidentiality and Loss of Privacy: All efforts will be made to ensure that subject information obtained during the course of this study will be kept confidential. However, we cannot guarantee total privacy. Personal information may be given out if required by law.

13.1.1 Protections Against Risks.

Weight Loss Intervention: Subjects will be informed of all potential risks when providing consent before enrolling in the study. They will be able to withdraw from the study at any time. Risk of gallbladder disease will be minimized by limiting weight loss to no more than 3 lb. per week for 3 consecutive weeks. Subjects who exceed this limit will be advised to increase their calorie intake.

Study Medication: As in previous studies conducted at the Center, [e.g., 58, 59, 79, 82, 112] we will make every attempt to minimize, assess, and manage the occurrence of any side effect or adverse event (AE) of the study medication. Subjects will be screened for medical conditions that would preclude the use of phentermine, and stringent exclusionary criteria will be employed to limit the possibility of AEs (see above). Subjects will be informed about the possibility of medication side effects, including symptoms of rare but serious conditions, during informed consent and prior to randomization to medication or placebo (for randomization-eligible subjects who lose < 2% after 4 weeks of BT). A list of the subject's current medications will be collected during the screening, and subjects will be asked to inform study staff before starting any new medication during the course of the study.

To reduce the likelihood of side effects, randomized subjects will be taught how to properly perform the subcutaneous injection of the study medication (phentermine or placebo), and the medication will be initiated at 0.6 mg/day and increased by 0.6 mg at weekly intervals until a dosage of 3.0 mg/day is achieved. Subjects who do not tolerate an increased dose during escalation will delay escalation by up to 7 days. Subjects will be instructed, if they miss a dose, to resume the once-daily regimen with the next scheduled dose and not to take an extra or higher dose. If they miss more than 3 days, they will be instructed to call the study medical staff who will re-initiate therapy at 0.6 mg/day to avoid gastrointestinal symptoms. Subjects will be taught how to properly store the medication and dispose of needles.

Randomized subjects will be asked to report any new symptoms to the research staff. In addition to assessment visits, randomized subjects will have a brief medical visit (10-15 minutes) with study staff (e.g., registered nurse) at week 2 (after initiation of the medication) and week 6 (after most subjects will have completed dose escalation) to monitor response to the medication. Side effects will be queried during every

study visit, and the study NP or physician will be available to assess the subject and evaluate and treat any adverse events. Subjects will be encouraged to contact study staff immediately should an AE occur between visits, and 24-hour contact information will be provided for study personnel and the study physician. If any AE requires treatment follow-up, subjects will be provided with appropriate referrals. For all non-study-related medical events, subjects will be referred to their own primary care provider.

During outcome assessments and brief medical visits, patients will be asked about their mood or any thoughts of harming themselves through administration of the Columbia-Suicide Severity Rating Scale. Additionally, online questionnaires assessing depressive symptoms will be checked within 24 hours of their completion for signs of severe depression, including suicidal ideation. (Participation in a weight loss program is not a risk factor for depression and typically results in improvements in mood. [113]) In the event of mental health events, subjects will be referred to the study's psychologist or psychiatrist for further evaluation to determine if clinical intervention is needed (i.e., referral to a mental health provider).

Subjects of childbearing potential will provide a urine pregnancy test during their initial assessment and again prior to randomization to a study medication and must agree in writing to use an approved method of contraception throughout the study. Approved methods include the use of double barrier methods (condom with spermicide or diaphragm with spermicide), stable hormonal contraception, intrauterine device, abstinence, or tubal ligation. Subjects will be asked to immediately notify the study team, discontinue the drug (if applicable), and consult with an obstetrician if they become pregnant during the study. Subjects who become pregnant will be withdrawn from the study medication and BT treatment. The study physician or NP will follow up with any such patients during pregnancy and after childbirth to assess adverse events.

Randomized subjects will have the option to stop taking study medication at any time. The PI or study physician may also withdraw a subject from the medication if medically appropriate. Stopping study medication will not preclude subjects' completion of the BT program (unless weight loss is contraindicated).

Confidentiality and Loss of Privacy: All applicable national and international guidelines, regulations, and Institutional Review Board (IRB) guidelines regarding subject privacy and confidentiality will be followed throughout the study. No identifying information will be included with stored research data, biological samples, clinical data, or reports of results. Penn network firewalls prevent unauthorized internal access to data, external access to data, and malicious intent to destroy data and systems. Controlled user access will ensure that only appropriate and authorized personnel are able to view, access, and modify study data. Data sent to the IRB, Investigational Drug Services, or the Data and Safety Monitoring Board will contain no identifying information, except as required when reporting AEs. Password-protected files linking subject names and ID numbers will only be accessible to the PI and research coordinator, and will be stored in a locked office. Publications will be based on analyses of de-identified data, and subject ID numbers will only be included if necessary to clarify an individual patient event. Patient privacy will be protected by conducting all assessments and treatment visits in closed examination rooms or offices, where only the patient and appropriate staff member are present. Subjects will not be video or audiotaped at any point during the study.

Biological Sample Storage: All samples and medication will kept in a secure refrigeration room accessible only to relevant study staff. Biological samples stored for later analysis will be labeled with the patient ID and relevant assessment code, and, after being centrifuged and separated, will be frozen at −80 °C.

13.2 Benefits

All subjects will receive 7 months of intensive behavioral weight loss treatment. Previous studies suggest that the average patient will achieve losses of 5-8% of initial weight and corresponding improvements in cardiometabolic risk factors (e.g., blood pressure, waist circumference, HDL cholesterol, triglycerides, glucose). Early non-responders to BT, who are unlikely to experience these benefits with continued BT alone, may be more likely to achieve these outcomes when medication is added to BT. This study will inform clinical best practice recommendations for prescribing BT or obesity pharmacotherapy by identifying characteristics of individuals who are not likely to lose weight with BT alone and providing preliminary data regarding whether such individuals benefit from the addition of obesity medication. These data could ultimately result in the development of algorithms that match obesity treatment methods to patient characteristics.

13.3 Risk Benefit Assessment

The anticipated risks of the study are minimal, and the potential benefits outweigh the risks.

13.4 Informed Consent Process / HIPAA Authorization

All applicants will be screened by phone to determine whether they potentially meet eligibility criteria. We will obtain a waiver of written documentation of consent for the telephone screen. Initially-eligible individuals will be invited for an in-person screening visit that will include a behavioral evaluation conducted by a psychologist (including the PI) and a medical history. These assessments will take place individually in staff offices and medical assessment rooms, respectively, to ensure patient privacy. During the behavioral evaluation, psychologists will explain the study procedures and possible risks and benefits associated with participation, including possible assignment to study medication or placebo during the randomized phase of the trial. Psychologists will inform subjects that their participation in the study is voluntary and that they will not lose any benefits to which they are otherwise entitled by choosing not to participate. They will offer to provide suggestions for alternative weight control programs if the individual chooses not to participate. After reviewing all study procedures, the subject will be given the opportunity to ask questions and additional time to review consent forms, if desired. The psychologist will obtain a signed consent and HIPAA authorization from interested and eligible subjects. Subjects will receive a copy of the combined consent/HIPAA form. The original signed consent/HIPAA forms will be stored in a regulatory consent binder. Final eligibility for enrollment will be determined by results of the behavioral evaluation, medical history, urine pregnancy test, and blood panel analysis.

At the randomization visit, trained research staff will review with subjects eligible for randomization (i.e., those who lose < 2% after 4 weeks of BT) information related to the study medication, including possible risks and benefits, and will confirm applicants' willingness to participate prior to enrolling them in the randomized phase of the trial.

14 Study Finances

14.1 Funding Source

We anticipate receiving funding for this study from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)'s K23 Mentored Patient-Oriented Research Career Development Award (Independent Clinical Trial Required) for the application "Improving Weight Loss in Early Non-responders to Behavioral Treatment" (K23DK116935-01A1).

14.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

14.3 Subject Stipends or Payments

Subjects will receive $75 after completing the post-treatment assessment visit (week 24) for the subject's time and effort of being in the trial.

15 Publication Plan

We will register the study with a publicly assessable database such as clinicaltrials.gov. The PI holds the primary responsibility for publication of the results of the study. An initial report of the findings will be presented at an annual scientific meeting (e.g., The Obesity Society, The Society for the Study of Ingestive Behavior, The Society for Behavior Medicine). We plan to publish the study results approximately 6 months after study completion in an appropriate journal (e.g., the New England Journal of Medicine, Obesity, International Journal of Obesity). Secondary papers will include an examination of behavioral and psychosocial predictors of weight loss.

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17 Attachments

- Sample Consent Form
- Questionnaire Measures