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Lorcaserin plus lifestyle modification for weight loss maintenance: Rationale and design for a randomized controlled trial

Jena Shaw Tronieri[a,*], Nasreen Alfaris[a], Ariana M. Chao[a,b], Rebecca L. Pearl[a], Naji Alamuddin[a,c], Zayna M. Bakizada[a], Robert I. Berkowitz[a,d], Thomas A. Wadden[a]

[a] Center for Weight and Eating Disorders, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, United States
[b] Department of Family and Community Health, School of Nursing, University of Pennsylvania, United States
[c] Institute for Diabetes, Obesity, and Metabolism, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, United States
[d] Department of Psychiatry and Behavioral Sciences, Children's Hospital of Philadelphia, Philadelphia, PA, United States

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ABSTRACT

Background/aims: Few studies have examined the efficacy of recently approved medications for chronic weight management in facilitating the maintenance of lost weight. This paper provides an overview of the design and rationale for a trial investigating whether lorcaserin, when combined with behavioral weight loss maintenance sessions (WLM), will facilitate the maintenance of losses of ≥ 5% of initial weight.

Methods: In this two-phase trial, participants with obesity will enroll in a 14-week run-in diet program consisting of weekly group lifestyle modification sessions and a 1000–1200 kcal/d meal replacement diet. Participants who complete this weight induction phase and lose at least 5% of initial weight will then be randomized to 52 weeks of WLM plus lorcaserin or WLM plus placebo. We hypothesize that at 52 weeks post randomization, participants assigned to WLM plus lorcaserin will achieve significantly better maintenance of the prior 5% weight loss.

Results: We will recruit 182 adults with obesity to participate in the diet run-in, 136 of whom (75%) are expected to become eligible for the randomized controlled trial. Co-primary outcomes include the percentage of participants who maintain a loss of at least 5% of initial weight at week 52 and change in weight (kg) from randomization to week 52.

Conclusions: This two-phase design will allow us to determine the potential efficacy of chronic weight management using lorcaserin for maintaining initial losses of at least 5% body weight, induced by the use of a structured meal-replacement diet. This combined approach holds promise of achieving larger long-term weight losses.

Clinical Trial Registration: NCT02388568 on ClinicalTrials.gov

1. Introduction

Comprehensive behavioral weight control interventions reliably induce mean losses of 5%–10% of initial weight [1]. Weight loss, however, is typically followed by steady regain over time [2,3]. Two interventions consistently prevent weight regain. The first is monthly or twice monthly weight loss maintenance (WLM) sessions, which support patients' continued efforts to consume a reduced-calorie diet, monitor their body weight regularly, and engage in high levels of physical activity (200–300 min/week) [1,4–6]. The second is the use of medications approved for chronic weight management [7]. Pharmacotherapy traditionally has been used to induce weight loss but may be of greater benefit in facilitating its maintenance [7,8]. The use of chronic weight management medications is analogous to the long-term (i.e., indefinite) use of medications to control hypertension and type 2 diabetes [9].

Since 2012, the U.S. Food and Drug Administration (FDA) has approved four new medications for chronic weight management [7,8]. They include two monotherapies: lorcaserin (Belviq), a selective serotonin receptor agonist [10]; and liraglutide 3.0 mg (Saxenda), a glucagon-like-peptide 1 (GLP-1) receptor agonist [11]. Two other new drugs represent combinations of medications originally approved for other purposes: phentermine-topiramate (Qsymia) and naltrexone-bupropion (Contrave) [12,13]. A fifth medication, orlistat (Xenical), received FDA approval was approved in 1999 for long-term weight management [14]. Table 1 summarizes the mechanisms of actions, side-effects, and efficacy of these medications.

Only two studies have examined the efficacy of these recently approved medications in facilitating the maintenance of lost weight

* Corresponding author at: 3535 Market Street, 3rd floor, Philadelphia, PA 19104, United States.
E-mail address: jenashaw@mail.med.upenn.edu (J.S. Tronieri).

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Table 1
Pharmacotherapy currently approved for chronic weight loss.

Drug (generic)	Dose	Mechanism of action	Mean placebo-subtracted weight loss, % or kg[a]; duration of trial	Common side effects	Contraindications
Orlistat, prescription (120 mg)	120 mg TID	Pancreatic and gastric lipase inhibitor	2.9–3.4 kg, 2.9–3.4%; 1 y	Decreased absorption of fat-soluble vitamins, steatorrhea, oily spotting, flatulence with discharge, fecal urgency, oily evacuation, increase defecation, fecal incontinence	Cyclosporine (taken 2 h before or after orlistat dose), chronic malabsorption syndrome, pregnancy and breastfeeding, cholestasis, levothyroxine, warfarin, antiepileptic drugs
Orlistat, over-the-counter (60 mg)	60–120 mg TID	Pancreatic and gastric lipase inhibitor	2.9–3.4 kg, 2.9–3.4%; 1 y	See orlistat, prescription	See orlistat, prescription
Lorcaserin	10 mg BID	$5HT_{2C}$ receptor agonist	3.6 kg, 3.6%; 1 y	Headache, nausea, dry mouth, dizziness, fatigue, constipation	Pregnancy and breastfeeding Use with caution: SSRI, SNRI/MAOI, St John's Wort, triptans, bupropion, dextromethorphan
Phentermine (P)/ topiramate (T)	3.75 mg P/23 mg T ER QD (starting dose) 7.5 mg P/46 mg T ER QD (recommended dose) 11.25 mg P/69 mg T ER daily 15 mg P/92 mg T ER QD (high dose)	GABA receptor modulation (T) plus norepinephrine-releasing agent (P)	6.6 kg (recommended dose), 6.6% 8.6 kg (high dose), 8.6%; 1 y	Insomnia, dry mouth, constipation, paresthesia, dizziness, dysgeusia	Pregnancy and breastfeeding, hyperthyroidism, glaucoma, MAOIs, sympathomimetic amines
Naltrexone (N)/ Bupropion (B)	32 mg N/360 mg B BID	Reuptake inhibitor of dopamine and norepinephrine (B) and opioid antagonist (N)	4.8%	Nausea, constipation, headache, vomiting, dizziness	Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal, MAOIs
Liraglutide	3.0 mg injectable	GLP-1 agonist	5.8 kg; 1 y	Nausea, vomiting, pancreatitis	Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history

Abbreviations: GABA, γ-aminobutyric acid; HR, heart rate; MAOI, monoamine oxidase inhibitors.
Table is reprinted with permission from reference [15].
[a] Mean weight loss in excess of placebo as percentage of initial body weight or mean kilogram weight loss over placebo.

[10,16], and only one examined their efficacy following weight loss achieved with behavioral weight control alone. In that trial, to qualify for randomization to drug or placebo, participants first had to lose 5% of initial weight by consuming a 1200–1400 kcal/d diet, which included three servings a day of liquid meal replacements [16]. The diet was combined with lifestyle counseling from a registered dietitian and provided for variable lengths of time (4–12 weeks) until participants lost 5%. Upon doing so, they were randomly assigned to liraglutide or placebo, both combined with 17 individual (15–20 min) WLM sessions over the ensuing 56 weeks. Significantly more liraglutide- than placebo-treated patients maintained the 5% weight loss at week 56 (81.4% vs 48.9%, $p < 0.001$). Moreover, participants assigned to liraglutide lost an additional 6.2% of body weight during the 56-week trial, compared with 0.2% for placebo [16].

The present study extends these findings by inducing a larger initial weight loss during the diet run-in program, before randomly assigning patients to drug or placebo. In this trial, all participants will be provided a 14-week group lifestyle modification program that includes the consumption of a 1000–1200 kcal/d meal-replacement diet. Participants must lose at least 5% of initial weight to be eligible for randomization to the 1-year weight loss maintenance study. However, participants are expected, on average, to lose approximately 10% of initial weight during the diet run-in [17], thus, potentially yielding large long-term weight losses. We chose to use lorcaserin in the present study because it is well tolerated and has not been examined when combined with a robust program of lifestyle modification [10].

2. Methods

2.1. Study design

This study is a two-phase, double-blind, parallel-group randomized controlled trial (Fig. 1). Phase I will consist of a non-randomized, 14-week group lifestyle modification program with a structured meal replacement diet. Those who lose ≥ 5% of initial weight will be eligible for Phase II (52 weeks) and will receive WLM sessions combined with lorcaserin or placebo. We hypothesize that at 52 weeks post randomization, the group assigned to WLM plus lorcaserin will achieve significantly better maintenance of the prior 5% weight loss than the WLM plus placebo group.

This trial is being conducted in an urban university medical center, and participants will be recruited from the greater metropolitan area. The study is supported by an investigator-initiated grant from Eisai Pharmaceuticals.

2.2. Phase I eligibility

A complete list of inclusion and exclusion criteria can be found in Table 2. Individuals are eligible for Phase I if they: are aged ≥ 21 years and ≤ 65 years; have a body mass index (BMI) ≥ 33 kg/m^2 and ≤ 55 kg/m^2 (or ≥ 30 kg/m^2 with an obesity-related comorbidity); and have a primary care provider responsible for their routine care. Eligible female participants cannot be pregnant or nursing and must agree to use a reliable form of contraception during the study. Participants will be excluded if they have medical conditions listed in Table 2, take medications known to affect weight, or have recently lost weight. Individuals taking medications that could interact with lorcaserin will also be excluded, as will persons with current major depression or who report a recent history of significant psychological symptoms. Participants will be instructed to continue taking prescribed medications to control non-excluded co-morbid conditions (e.g., hypertension, hypercholesterolemia). Eligible participants are expected to have been on their medication regimen (including the dose) for 3 months prior to beginning Phase I treatment.

2.3. Recruitment and screening

Participants will be recruited from advertisements in local media (i.e., newspapers, radio) and flyers posted at the university. We will also advertise the study to our university-based health care providers. Telephone prescreening of respondents will be used to assess preliminary eligibility and interest in the study. Individuals who appear eligible will then be scheduled for an in-person screening visit and asked to complete the Beck Depression Inventory (BDI-II) [18] and the Weight and Lifestyle Inventory (WALI) [19], a paper-and-pencil questionnaire that assesses eating and activity behaviors. The in-person screening will be conducted by a psychologist, who will obtain informed consent and evaluate participants' behavioral eligibility (i.e., willingness and appropriateness to participate). This includes the assessment of the applicant's mood (as evaluated by interview and the BDI-II) and suicidality (including history of suicidal ideation and behavior, as assessed by the Columbia-Suicide Severity Rating Scale; C-SSRS) [20].

Participants who pass this portion of the screening assessment and remain interested will then meet with the study's nurse practitioner or physician, who will obtain a medical history and conduct a physical examination to determine medical eligibility. Persons who remain eligible will then have an electrocardiogram (EKG), fasting blood test, and urine pregnancy test (for females of child-bearing age) to determine that final eligibility criteria are met. Individuals who pass all screening assessments (and still wish to participate) will be considered enrolled and will be scheduled to attend the Phase I program.

2.4. Phase I: weight loss intervention

During the weight loss induction phase, participants will attend 14 weekly, 90-minute (in-person) group lifestyle modification sessions. Groups will consist of 10 to 15 participants and will be led by registered dieticians or psychologists. Individuals who miss a group meeting will be encouraged to attend a makeup visit.

The lifestyle intervention manual was adapted from previous behavioral protocols developed by Wadden et al. [17,21]. Session topics are based on cognitive behavioral principles such as self-monitoring, stimulus control, behavioral analysis, goal-setting, problem-solving, cognitive restructuring, and relapse prevention. Throughout the treatment, participants will be asked to record all foods and drinks consumed (including amounts and calories) and to record their weight weekly at home. They will be encouraged to use online tracking apps (e.g., MyFitnessPal) to facilitate recording. Participants will be instructed to gradually increase their physical activity to 175 min/week by week 14.

During Phase I, participants will be prescribed a structured meal replacement diet that provides 1000–1200 kcal per day [17,21]. During the first week, they will be asked to record their food intake and prepare their home environment (e.g., purchase fruits and vegetables, remove other foods from the home). From weeks 2 to 12, they will be instructed to consume four servings daily of a liquid shake (Health Management Resources – HMR; 160 kcal per shake), a prepackaged (or frozen) food entrée (250–300 kcal), 1–2 servings of fruit, and a salad. All HMR products (liquid shakes and prepackaged entrées) will be provided free of charge. From weeks 12–14, participants will be prescribed a re-feeding diet that gradually replaces the consumption of shakes with conventional foods, so that the use of shakes is terminated by week 14.

Although the minimum weight loss required for Phase II eligibility is ≥ 5% of initial weight, participants will be told to expect a greater weight loss (approximately 10% of initial weight) and encouraged to lose as much as possible at a safe rate of 0.5–1.5 kg per week. However, persons with a BMI < 30 kg/m^2 (or 27 kg/m^2 with an obesity-related co-morbidity) potentially are not eligible to initiate pharmacotherapy for weight loss. Therefore, participants who reach a BMI of 30.5 kg/m^2

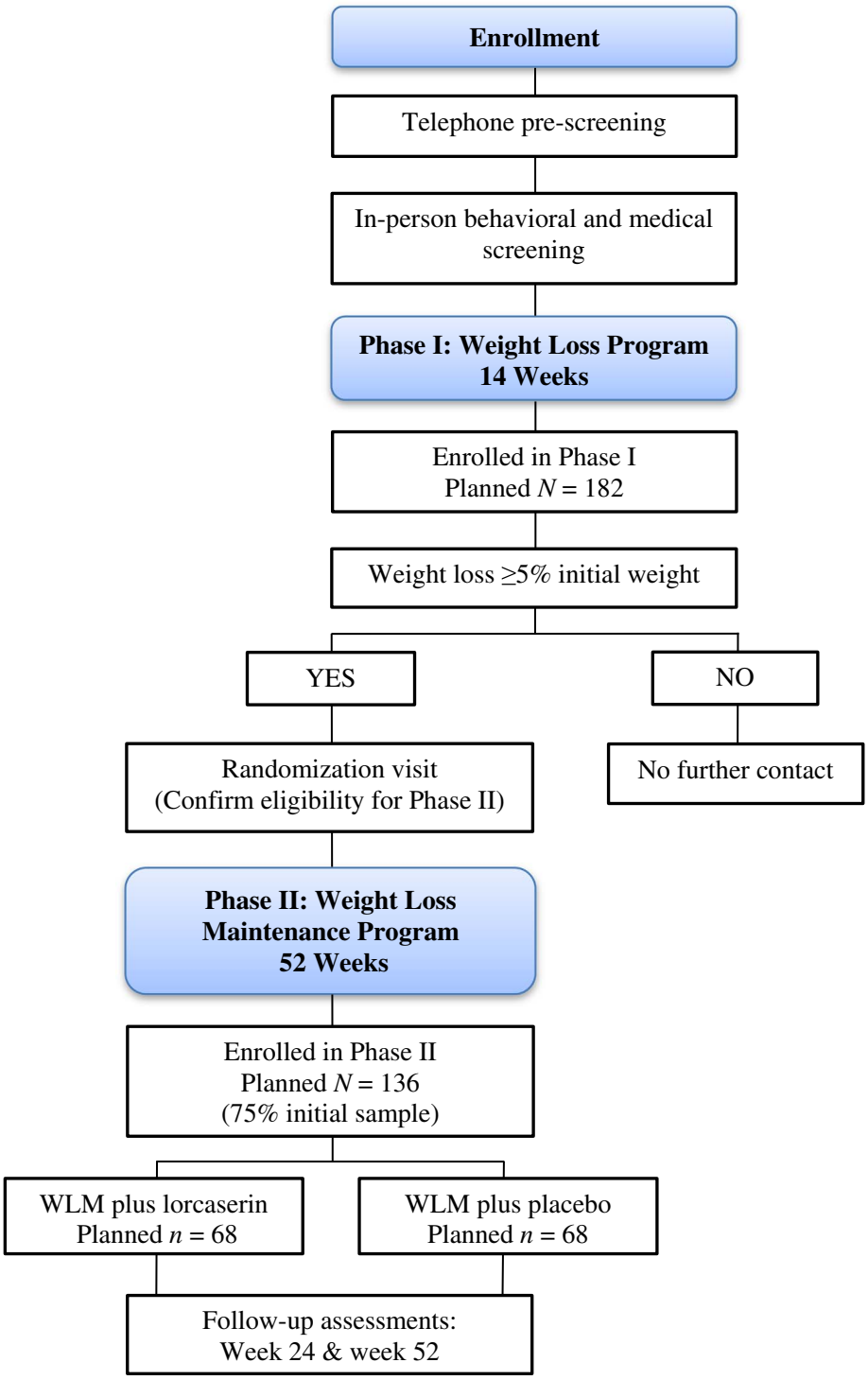

Fig. 1. Proposed participant flow through study.

(27.5 kg/m^2 with co-morbidity) during Phase I will be encouraged to slow their rate of weight loss so that they remain eligible for Phase II of the study. Such individuals will be told that they can resume active weight loss, if desired, once the second phase has begun.

2.5. Randomization

Participants will be randomly assigned to treatment conditions (lorcaserin or placebo) after they complete Phase I and lose ≥ 5% of initial weight. We considered randomizing participants at the beginning of the run-in period, but decided against this design because chance differences in weight loss might emerge between groups during the run-in phase [22,23]. Such differences make it difficult to determine whether later differences in weight loss between conditions (or lack thereof) are attributable to the treatment interventions or to the initial differences in weight loss during the run-in phase. Because of the potential for cohort effects in obesity treatment [24], participants will be assigned to treatment conditions individually rather than by group cohort.

Randomization will be conducted by the Investigational Drug Service at the University, which will assign treatment condition in blocks of 6 participants via a random number generator. Both participants and study personnel will be blind to participant's treatment status. Qualifying participants will begin taking study medication

Table 2
Inclusion and exclusion criteria.

Inclusion criteria for Phase I
1. Age ≥ 21 years and ≤ 65 years
2. BMI ≥ 33 kg/m^2 and ≤ 55 kg/m^2 or ≥ 30 kg/m^2 with an obesity-related comorbidity (e.g., hypertension, dyslipidemia)
3. Have a primary doctor responsible for routine care
4. Female participants will be:
a. non-pregnant, evidenced by a negative urine dipstick pregnancy test
b. non-lactating
c. surgically sterile or postmenopausal, or will agree to use an accepted method of birth control during the study
Exclusion criteria for Phase I
1. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg, or diastolic blood pressure ≥ 100 mmHg)
2. Type 1 diabetes or type 2 diabetes
3. Fasting glucose ≥ 126 mg/dl or HbA1c ≥ 6.5%
4. Recent history of cardiovascular disease (e.g., myocardial infarction or stroke within the past 6 months), congestive heart failure, or heart block greater than first degree
5. Clinically significant hepatic or renal disease
6. Thyroid disease not controlled
7. History of malignancy (except for non-melanoma skin cancer)
8. Use of medications known to induce significant weight loss/gain, such as oral steroids
9. Loss of ≥ 10 lb within the past 3 months
10. History of (or plans for) bariatric surgery
11. Current major depressive episode, active suicidal ideation, or history of suicide attempts
12. Use of monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclics, lithium, triptans, antipsychotics, cabergoline, linezolid, tramadol, dextromethorphan, tryptophan, bupropion, St. John's Wort, or medicines to treat erectile dysfunction
13. Psychiatric hospitalization within the past 6 months
14. Self-reported alcohol or substance abuse within the past 12 months, including at-risk drinking (current consumption of ≥ 14 alcoholic drinks per week)
Inclusion criteria for Phase II
1. Weight loss of at least ≥ 5% initial body weight during Phase I
2. Randomization BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with an obesity-related comorbidity
3. Continue to meet all other Phase I inclusion and exclusion criteria

within a week of their randomization visit. They will be instructed to take two doses per day of either lorcaserin (10 mg) or placebo.

2.6. Phase II: weight loss maintenance intervention

During the maintenance phase, qualifying individuals will continue to attend group lifestyle modification sessions every-other-week for the first 12 weeks (i.e., 6 sessions) and once every 4 weeks for the remainder of the 52-week period (i.e., 10 sessions). For patient convenience, approximately every other session will be delivered via group conference call. Participants, however, can elect to attend sessions in person on those weeks. Phone-delivered lifestyle counseling is as effective as face-to-face counseling for both the induction and maintenance of weight loss [4,25].

In addition to the behavioral principles covered in Phase I, WLM sessions will include nutrition recommendations following current dietary guidelines (i.e., MyPlate) [26] and weight loss maintenance strategies. Participants will be encouraged to consume a diet of conventional foods, and no additional meal replacement products will be provided. Individualized calorie goals will be provided based on participants' body weights and whether they desire to lose additional weight or to maintain their weight. Participants will be encouraged to continue recording their food intake and weighing themselves at least once per week. They will continue to increase their physical activity to 225 min/week by week 40 to facilitate the maintenance of lost weight.

2.7. Safety monitoring

To monitor safety, participants will have a physical examination, fasting blood test, and urine pregnancy test (for women capable of becoming pregnant) at week 8 of Phase I; at the randomization visit after completion of Phase I; and at weeks 24 and 52 of Phase II. Suicidal ideation also will be re-assessed at these times using the C-SSRS [20]. An EKG will be repeated at randomization and as needed at other assessment points.

Ongoing safety monitoring will occur at approximately every-other-treatment session throughout both phases. Ongoing monitoring will consist of a brief medical visit with the study physician or nurse practitioner in which vital signs will be measured (i.e., blood pressure and pulse), the C-SSRS will be administered, and any reported adverse events assessed. A final brief medical visit will be completed at week 56 to assess participants' health after terminating medication at week 52.

Randomized participants will have the option to stop taking study medication at any time. The PI or study physician may also withdraw a participant from the medication if medically appropriate. Adherence to the medication regimen will be assessed by asking participants to return medication containers, including any unused medication, to the study team at each safety monitoring visit. All randomized participants, regardless of medication withdrawal or non-adherence, will be invited to complete the group WLM program and will be included in the study's primary analyses.

2.8. Study outcomes

The primary study outcome is the maintenance of weight loss from randomization to week 52, defined as the percentage of participants who maintain the loss of 5% or more of initial weight achieved during Phase I. The co-primary outcome is the change in weight (kg) from randomization to week 52. Secondary outcomes include percentage of participants who maintain a loss of 10% or more of initial weight at week 52, average percentage reduction in initial weight (from randomization to week 52), as well as change in cardiometabolic risk factors and psychosocial measures, as described below.

2.8.1. Body weight

Body weight will be measured at all clinic visits and at each outcome assessment on a digital scale (to the nearest 0.1 kg) with participants dressed in light clothing, without shoes. Two measurements will be taken at each outcome assessment. Participants' heights will be measured to the nearest 0.1 cm using a calibrated, wall-mounted stadiometer (two measurements), BMI will be calculated as the ratio of kg/m^2.

2.8.2. Cardiometabolic risk factors

Blood pressure and pulse will be measured using an automated monitor (Dinamap, model 9300). Two readings will be taken on each occasion (at 1-minute intervals), after participants have been seated for at least 5 minutes [27]. Fasting blood samples taken at each outcome assessment will be assayed for a complete blood count, comprehensive metabolic panel, lipid panel, hemoglobin A1c, insulin, and high sensitivity C-reactive protein. Waist circumference will be measured to the nearest 0.1 cm halfway between the lowest rib and the top of the hipbone [27]. Two measurements will be obtained at each outcome assessment.

2.8.3. Psychosocial measures

Questionnaire packets will be completed at screening, randomization, and weeks 24 and 52 of Phase II. Mood will be assessed using the Patient Health Questionnaire [28] and BDI-II [18], and stress by the Perceived Stress Questionnaire [29]. Quality of life will be evaluated using the SF-36 [30] and Impact of Weight on Quality of Life – Lite [31]. Cognitive restraint, disinhibition, and hunger will be assessed using the Eating Inventory [32] and visual analogue scales [33]. Food addiction will be measured using the Yale Food Addiction Scale [34] and food cravings by the Food Craving Inventory [35]. Binge eating will

be assessed by the Eating Disorder Examination-Questionnaire [36]. Physical activity will be measured by the Paffenbarger Physical Activity Survey [37].

2.9. Statistical analysis

2.9.1. Sample size justification

A power analysis was conducted based on the co-primary endpoints: 1) change in body weight (in kg) from randomization to week 52, and 2) the percentage of participants in the two groups that, at week 52, maintain the ≥ 5% reduction in body weight achieved during Phase I. Estimates of mean weight change for placebo-treated participants are based on prior studies we and others have conducted, e.g., [10–14,16], while estimates for lorcaserin are based on findings from studies of sibutramine and liraglutide that have used similar run-in designs [16,38–39]. We predict a difference in weight change between the two groups (from randomization to month 12) of 3 kg (SD = 5.0, ICC = 0.80). We anticipate mean weight changes at week 52 of "0" kg for lorcaserin and "+ 3" kg for placebo. (This is a conservative prediction; we believe that lorcaserin treated participants may lose a mean of 1–2 kg, while those treated by placebo may gain 4–5 kg). Furthermore, we predict that 80% of the lorcaserin participants will have maintained the ≥ 5% reduction in body weight from randomization through the 52 week assessment, as compared to only 50% of the placebo group.

Based on Holm's adjustment for multiple comparisons [40], the smaller of the two *p* values resulting from analyses of our two primary contrasts will be compared at alpha equal to 0.025 and, if significant, the other contrast will be evaluated at 0.05. Consistent with this form of Type I error control, study power is estimated as the probability of at least one significant contrast.

Final sample size estimates consider probable rates of Phase I completion and Phase II attrition based on studies that have used similar run-in designs [16,38–39]. The planned Phase II sample size of 136 participants randomized in a 1:1 ratio to lorcaserin or placebo is estimated to be adequate to evaluate the two co-primary end points with a combined power of at least 80% (two-sided tests). This estimate allows for 20% attrition during the 52-week randomized trial, resulting in approximately 54 treatment completers in arm. In order to achieve this sample size, we plan to recruit 182 participants for Phase I, of whom 75% are expected to lose ≥ 5% of initial weight and be eligible for randomization.

2.9.2. Primary analyses

Data quality and integrity will be checked by assessing the data for missing and out-of-range values with basic statistical procedures, including univariate statistics and visual graphical displays (e.g., scatter plots). To test the adequacy of randomization, preliminary analyses will include a comparison of demographic and baseline characteristics between randomized treatment groups (lorcaserin and placebo; *t*-tests or Wilcoxon rank sum tests for continuous variables and Chi-Square test or Fisher's Exact test for categorical data). If imbalances are observed, the relevant variables will be included as covariates in the final analyses.

For the comparison of the percentage of participants in the two treatment groups that, at week 52, maintained a ≥ 5% reduction in body weight, we will use generalized estimating equations (GEE) to fit population-averaged logistic models assuming the binomial distribution. Nested mixed models will be used to compare the co-primary outcome of weight change from randomization to week 52. All data will be analyzed under the intention-to-treat principle (ITT). In fitting the mixed effects model with residual maximum likelihood (REML), a variance-covariance structure will be selected based on criteria such as the Akaike's Information Criterion (AIC). These models will contain fixed main effects for change from baseline (at the start of Phase I) to each follow-up visit (including both Phase I and Phase II visits), group (lorcaserin or placebo), and the interaction between visit and group. The primary focus will be on the 52-week comparison. Analyses will be two-tailed with a significance level of 0.05, and will be conducted using SPSS version 24.0 or SAS version 9.4.

All randomized participants will be included in the primary ITT analyses. Assuming adequate fit of the mixed effects models to the data, the proposed 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 [41]. Within GEE and mixed effects models, missing data are handled by way of maximum likelihood and the missing at random assumption. Prior to conducting final analyses, we will examine the assumption of data missing at random and 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. In the case that data cannot be assumed to be missing completely at random, we will consider imputing missing endpoint data using multiple imputation techniques, fitting selection models, and fitting pattern mixture models.

A modified ITT analysis also will be conducted including only those participants who receive at least one dose of medication and provide at least one post-randomization body weight measurement. A per protocol analysis will be conducted that includes only participants who provide a measurement of body weight at week 52 (within ± 4 weeks). Secondary end point evaluations will be based on two-sided testing at a 5% significance level, and similar analytic strategies will be employed.

3. Discussion

This randomized controlled trial will test whether lorcaserin plus WLM counseling enhances the maintenance of initial weight loss, as compared to placebo plus WLM. We anticipate that the use of meal replacements during a 14-week diet run-in will result in large initial losses (at least 5% and approximately 10% on average), which we hypothesize will be better maintained at week 52 with lorcaserin than with placebo. If successful, this treatment combination could help to address the problem of weight regain that typically follows an initial course of lifestyle modification [2]. In addition, the inclusion of an initial meal replacement diet, which has been shown to boost weight loss [42–43], may improve the size of the weight loss produced by lorcaserin in previous studies (i.e., 5.8%) [11]. Weight losses of 10% or more of initial weight are desired by patients and are associated with greater improvements in cardiometabolic risk factors than are smaller losses [1].

Lorcaserin could increase mean long-term weight loss in an additive manner, above the expected 10% mean reduction achieved during the 14-week diet run-in program. Such additive weight loss was observed when participants who had lost an average of 6 kg during a diet run-in were provided liraglutide 3.0 [16]. They lost an additional 6 kg after 1 year on medication, as compared to a loss of 0.2 kg for participants assigned to placebo. This 5.8 kg placebo-subtracted difference is very similar to liraglutide's effect when it is used for the induction (rather than maintenance) of weight loss [11]. Sibutramine was observed to have a similar additive effect on weight loss maintenance, but the drug was removed from the market in 2011 because it increased the risk of cardiovascular morbidity and mortality [44]. In contrast to these two medications, orlistat was not found to have additive effects on weight loss maintenance when used either following an approximately 10–12 kg loss achieved with a diet run-in program [45] or following weight loss with sibutramine [46]. In the diet run-in study, participants actually regained 33% of their lost weight at the end of 1 year of taking orlistat, compared with a 59% regain for patients assigned to placebo [45].

The present study design will allow us to test lorcaserin's effectiveness in facilitating the maintenance of lost weight, as compared with its prior evaluations for inducing weight loss [10]. However, the study will not allow us to assess the effectiveness of lorcaserin used alone, without accompanying lifestyle modification, in promoting weight loss maintenance. Such an assessment would require two

additional treatment arms – lorcaserin with no lifestyle modification and placebo with no lifestyle modification. Our prior investigations, however, suggested that when weight loss medications are used alone, and not as an adjunct to diet and physical activity counseling, they produce about only one-half the weight loss as when they are combined with lifestyle modification [27,47]. Thus, we chose a clinical intervention (and experimental design) designed to maximize long-term weight loss.

Previous trials of long-term pharmacotherapy for obesity have reported high levels of attrition in both individuals who received active medication and those provided placebo [10,48]. We seek to reduce dropout in the present trial by offering all participants an active WLM intervention that has been shown to improve maintenance of lost weight in comparison to no treatment [4,5]. We also will invite participants who choose to discontinue study medication (for any reason) to continue to participate in the WLM program.

Pharmacotherapy traditionally has been tested as a method for inducing weight loss, and most maintenance trials have used designs that simply extend initial treatment assignments. This study tests whether use of a medication (lorcaserin) approved for chronic weight management will enhance long-term weight loss maintenance after successful weight loss with intensive lifestyle modification and meal replacements. We believe that the combination of large initial weight losses and maintenance treatments that include WLM and lorcaserin could potentially produce the long-term weight losses of 10% or more of initial weight that patients and their practitioners seek [49].

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Declaration of conflicting interests

T. Wadden discloses serving on advisory boards for Novo Nordisk, Nutrisystem, and Weight Watchers, as well as receiving grant support, on behalf of the University of Pennsylvania, from Eisai Pharmaceutical Co. None of the other authors declare any conflicts.

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