Protocol: Combining Lifestyle Modification and Liraglutide to Improve Weight Loss and Health Outcomes. Addendum to the Protocol in order to Study the Efficacy of Liraglutiude 3.0 mg/d Combined with Phentermine 15 mg/d to Increase Weight Loss in a 12-Week Placebo-Controlled Trial, Following Completion of the Original 1-Year Study

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Combining Lifestyle Modification and Liraglutide to Improve Weight Loss and Health Outcomes

Addendum to the Protocol in order to Study the Efficacy of Liraglutiude 3.0 mg/d Combined with Phentermine 15 mg/d to Increase Weight Loss in a 12-Week Placebo-Controlled Trial, Following Completion of the Original 1-Year Study

INVESTIGATOR-INITIATED STUDY PROTOCOL

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Department of Psychiatry
Perelman School of Medicine, University of Pennsylvania
3535 Market St # 3029
Philadelphia, PA 19104

Correspondence to:

Thomas A. Wadden, Ph.D.

Director, Center for Weight and Eating Disorders
Perelman School of Medicine,
University of Pennsylvania
3535 Market Street, Suite 3029
Philadelphia, PA 19104
Phone: 215-898-7314
Fax: 215-898- 2878
wadden@mail.med.upenn.edu

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BACKGROUND AND SIGNIFICANCE:

A 5–10% reduction in body weight in obese individuals improves several risk factors for cardiovascular disease (CVD) including elevated blood glucose, blood pressure, and plasma triglyceride concentrations.[1] Losses of this magnitude can be induced by a high intensity program of lifestyle modification (i.e., diet, physical activity, and behavior therapy) provided in 14 or more counseling sessions in 6 months. This is the frequency of group or individual counseling recommended by a recent NIH expert panel.[1] It also is the frequency of brief (10-15 minute), individual counseling prescribed and reimbursed by the Centers for Medicare and Medicaid Services (CMS).[2] Remarkably, the efficacy of the specific CMS model of counseling has not been evaluated.

A loss of 5-10% of initial weight also may be achieved with the use of pharmacologic agents,[3] including liraglutide 3.0,[4] lorcaserin,[5] combination naltrexone plus bupropion,[6] and combination phentermine plus topirimate.[7] Liraglutide 3.0 (Saxenda®) belongs to a class of medications called glucagon-like peptide-1 (GLP-1) receptor agonists. Liraglutide is a once-daily self-administered, subcutaneous (beneath the skin) injection that may reduce appetite and help overweight or obese adults lose weight and it off. Liraglutide is approved by the U.S. Food and Drug Administration (FDA) for chronic weight management, when combined with a reduced-calorie diet and increased physical activity.

Weight loss medications typically are used with a less intensive program of lifestyle modification (e.g., monthly visits), consistent with the limitations of busy primary care practices.[3] Adding weight loss medication to high intensity lifestyle modification typically results in a mean weight loss equal to the sum of the two separate interventions.[8] This finding was demonstrated with sibutramine in studies of both obese adults[8,9] and adolescents.[10] Wadden et al found that sibutramine alone (10-15 mg/d) reduced initial weight by 5% at 1 year in adults, compared with 7% achieved with high intensity lifestyle modification alone, and 12% resulting from the combination of the two therapies.[8] Berkowitz et al found that lifestyle modification alone produced a 4% reduction in initial weight in adolescents at 6 months, which increased to 8% with the addition of sibutramine.[10]

Larger weight losses of 10-15% of initial weight are associated with greater improvements in risk factors[11] and are more consistent with obese individuals' desired weight loss goals.[12, 13] Portion-controlled diets that provide 1000-1200 kcal/day (in the form of liquid shakes, meal bars, and prepared entrees) reliably induce mean weight losses that are 3 to 5 kg (and 3 to 5 percentage points) greater than losses achieved with an equivalent calorie diet comprised of conventional foods.[14, 15] This is because portion-controlled diets help patients come closer to meeting their prescribed calorie targets. Numerous studies have reported losses of 10-12% of initial weight in subjects who (for 12-16 weeks) consumed a 1000-1200 kcal/d diet in combination with intensive lifestyle modification.[16, 17]

The proposed 52-week randomized controlled trial will compare three treatment groups: 1) CMS lifestyle counselling (CMS-Alone); 2) CMS lifestyle counselling plus liraglutide (i.e., CMS-Liraglutide), and 3) CMS-Liraglutide plus a 1000-1200 kcal/day portion-controlled diet (i.e., Multi-Component Intervention). This is the first evaluation of the CMS-recommended schedule of lifestyle counselling (14 sessions in 26 weeks, followed by monthly sessions in weeks 27-52) and the first assessment of the benefits of adding liraglutide 3.0 to the CMS counselling program. The study will also assess the benefits of adding a portion-controlled diet to the combination of CMS lifestyle counselling and liraglutide, with a goal of achieving a mean weight loss of 14% or more of initial weight, similar to losses our research team produced with the triple combination of high intensity lifestyle modification, sibutramine, and a portion-controlled diet.[9]

Three factors suggest that the results of this study will significantly improve the management of obesity in primary care practice. **First**, this is the first trial to assess the efficacy of the CMS-recommended program of lifestyle modification for obesity, which includes 14 brief (15-minute) individual counseling sessions in 26 weeks, delivered by a physician, nurse practitioner, physician assistant, or registered dietitian (the latter working incident to the former practitioners).[2] Six additional monthly sessions are provided in weeks 27-52. The demonstration of the efficacy of this intervention, as indicated by the loss of approximately 5% of initial weight in 6 months, would facilitate the fuller adoption of this treatment model in primary care practice. Our research team also would facilitate this adoption by posting on a web site the lifestyle intervention that we will use, which is based on the Diabetes Prevention Program.[18] (CMS currently provides practitioners no recommendations for a lifestyle intervention protocol.) **Second,** the trial will demonstrate that practitioners can increase weight loss by 5% by combining CMS counseling with liraglutide 3.0 (i.e., Saxenda) and increase it further with the combination of liraglutide 3.0 plus a 1000-1200 portion-controlled diet (i.e., Multi-Component Intervention). Increased weight loss will be associated with a **third** benefit – greater improvements in CVD risk factors, mood, eating behavior, appetite, quality of life, sleep, and satisfaction with weight loss. Subjects who receive adjunctive therapy also will report greater satisfaction with their weight loss compared to individuals who receive CMS lifestyle counseling alone. Obese individuals would like to lose 25-35% of their initial body weight but report being generally satisfied after achieving losses of approximately 10% of baseline weight.[12, 13]

SPECIFIC OBJECTIVES:

Primary Objective

To compare the 52-week mean percentage reduction in initial weight achieved with CMS-Alone to that achieved with both CMS-Liraglutide and the Multi-Component Intervention.

Secondary Objectives

To compare the three interventions at week 52 in the proportion of subjects who lose ≥5%, ≥10%, and ≥15% of initial weight, as well as the % reduction in weight at week 24 and the proportion of subjects who meet the categorical weight losses at this time.

To compare the three groups at week 52 on changes in cardiovascular disease (CVD) risk factors (i.e, blood pressure, triglycerides, LDL and HDL cholesterol, C reactive protein, and waist circumference), glycemic control (i.e., fasting blood sugar, HbA1c, insulin, and HOMA), mood (PHQ-9), quality of life (i.e, SF-36 and IWQOL-Lite), eating behavior (i.e., Eating Inventory, Eating Disorder Examination-Questionnaire, and Yale Food Addiction Scale), appetite (i.e., visual analogue scales), sleep (i.e., Pittsburgh Sleep Quality Index), and weight loss satisfaction.

RESEARCH DESIGN AND METHODS:

Study Hypotheses:

Primary aim 1: To compare the 52-week mean percentage reduction in initial weight achieved with CMS-Alone to that achieved with both CMS-Liraglutide and the Multi-Component Intervention.

H_1: CMS lifestyle counseling combined with liraglutide will produce significantly greater mean weight loss at 52 weeks than will CMS-Alone (with expected mean losses of 9.5% and 5.0%, respectively). The Multi-Component Intervention (i.e., CMS counseling + liraglutide + portion-controlled diet) similarly will produce significantly greater mean weight loss at 52 weeks than will CMS-Alone (with expected mean losses of 14.0% and 5.0%, respectively).

The trial has the following **secondary aims and hypotheses**.

Aim 2: To compare the 52-week mean percentage reduction in initial weight achieved with the Multi-Component Intervention to that achieved with CMS-Liraglutide.

H_2: The Multi-Component Intervention will produce significantly greater mean weight loss at 52 weeks than will CMS-Liraglutide (with expected mean losses of 14.0% and 9.5%, respectively).

Aim 3: To compare the three treatment groups in the proportion of subjects who lose ≥5%, ≥10% and ≥15% of initial body weight at week 52.

H_3: A significantly greater proportion of subjects in the Multi-Component Intervention will meet the three categorical weight loss criteria (i.e., ≥5%, ≥10% and ≥15% loss) than will subjects assigned to CMS-Liraglutide which, in turn, will be superior to CMS-Alone.

Aim 4: To compare differences among the three treatment groups in the mean percentage reduction in initial weight at week 24, as well as the proportion of subjects who meet the three categorical weight loss criteria.

H_4: Subjects assigned to the Multi-Component Intervention will lose significantly more weight at 6 months than those assigned to CMS-Liraglutide which, in turn, will be superior to CMS-Alone. Achievement of categorical weight loss criteria will follow the same pattern.

Aim 5: To compare the three treatment groups on changes, as measured from randomization to week 52, in cardiovascular disease (CVD) risk factors (i.e, blood pressure, triglycerides, LDL and HDL cholesterol, C reactive protein, and waist circumference), glycemic control (i.e., fasting blood sugar, HbA1c, insulin, and HOMA), mood (PHQ-9), quality of life (i.e, SF-36 and IWQOL-Lite), eating behavior (i.e., Eating Inventory, Eating Disorder Examination-Questionnaire, and Yale Food Addiction Scale), appetite (i.e., visual analogue scales), sleep (i.e., Pittsburgh Sleep Quality Index), and weight loss satisfaction.

H_5: Subjects in the Multi-Component Intervention will achieve greater improvements on these secondary outcomes than will those assigned to CMS-Liraglutide which, in turn, will be superior to CMS-Alone. (We note that these latter comparisons are considered exploratory. The study is not powered to determine significant differences among groups on these outcomes.)

Endpoints:

Primary

The primary endpoint is change in body weight (i.e., % reduction in initial weight), as measured from randomization to week 52.

Secondary

Secondary endpoints include mean percentage reduction in initial weight as measured from randomization to week 24; the proportion of subjects who lose $\geq$5%, $\geq$10% and $\geq$15% of initial body weight as measured from randomization to week 52 and to week 24; and changes from randomization to week 52 in cardiovascular disease (CVD) risk factors (i.e, blood pressure, triglycerides, LDL and HDL cholesterol, C reactive protein, and waist circumference), glycemic control (i.e., fasting blood sugar, HbA1c, insulin, and HOMA), mood (PHQ-9), quality of life (i.e, SF-36 and IWQOL-Lite), eating behavior (i.e., Eating Inventory, Eating Disorder Examination-Questionnaire, and Yale Food Addiction Scale), appetite (i.e., visual analogue scales), sleep (i.e., Pittsburgh Sleep Quality Index), and weight loss satisfaction. (Please see Table 1 for study timeline and endpoint assessments.)

Study type:

This is a 52 week, single center, open-labeled, randomized controlled, parallel group design trial. Neither subjects nor investigators will be masked to treatment assignment.

A total of 150 subjects with obesity, who are free of types 1 and 2 diabetes, as well as contraindications to weight loss (described later), will be randomly assigned to one of three treatment groups: 1) CMS lifestyle counseling (CMS-Alone; N = 50); 2) CMS lifestyle counseling plus liraglutide (i.e., CMS-Liraglutide; N = 50); or 3) CMS-Liraglutide plus a portion-controlled diet (i.e., Multi-Component Intervention; N = 50).

Subjects in all three groups will have 14 brief (15 minute) lifestyle counseling visits the first 24 weeks, followed by monthly visits in weeks 25-52. This is the schedule and duration of counseling visits recommended by CMS.[2] Counseling sessions will be delivered by a nurse practitioner or registered dietitian (RD). (RDs are eligible to provide lifestyle counseling under CMS rules, when supervised by a primary care provider. In addition, in the U.S., the Affordable Care Act is likely to cover weight loss counseling as provided by RDs and a range of other trained interventionists.) Subjects in all three groups also will have brief physician visits at weeks 1, 4, 8, 16, 24, 36, and 52 (total of 7 visits). These visits are needed for subjects in both liraglutide groups to monitor their response to the medication. These visits are included for subjects in CMS-Alone to match the intensity of medical care provided the two other groups.

This is an open-label trial, the rationale for which is discussed in the next section (i.e., Rationale for Study Design).

The trial incorporates an additive treatment design, which will test the benefit of intensifying CMS counseling with the addition of liraglutide 3.0, as well as liraglutide 3.0 combined with a 1000-1200 kcal/day portion-controlled diet.

Individual subjects will receive lifestyle counseling for 52 weeks. The total study duration from time of first subject recruitment to data analysis and presentation of the first abstract will be 2.5 years. (Please see Table 2 for study timeline.)

Rationale for Study Design

The study design does not include the use of a placebo in comparing CMS-Alone to CMS-Liraglutide. This decision is based on multiple prior demonstration that liraglutide is superior to placebo (i.e., the medication's efficacy is not in question).[19] We plan to use liraglutide in the manner recommended by the U.S. Food and Drug Administration (FDA), by adding it to a program of diet and exercise counseling. We have conducted three previous studies in adults, which combined lifestyle modification with an FDA-approved weight loss medication (i.e., sibutramine). None of these studies included a placebo (i.e., they were open-label studies). **Two of the trials were published in the New England Journal of Medicine,[8, 20] and one in Archives of Internal Medicine.[9]**

Our study design also does not include assignment to a Usual Care group, against which to judge the efficacy of the CMS-Alone intervention (i.e., lifestyle counseling alone). We

have omitted a Usual Care group because of concerns that it does not meet current guidelines from the U.S. Preventive Services Task Force to "offer all obese individuals intensive lifestyle counseling."[21] Previous studies have shown that Usual Care induces a weight loss of approximately 1 kg at 1 year,[22] which potentially would present problems in retaining subjects in the study (i.e., they would drop out because of dissatisfaction with their weight change). The present study nonetheless will provide the first estimate (from a randomized controlled trial) of the weight loss that can be expected from CMS counseling.

The study design also does not include a treatment group that is assigned to CMS counseling combined with a portion-controlled diet alone, without liraglutide. Numerous prior studies have demonstrated that low-calorie, portion-controlled diets increase weight loss as compared with a diet of conventional foods.[14, 15, 23] We do not think there is a need to replicate this finding in the present study. Instead, we wish to focus this trial on inducing and maintaining large weight losses (≥ 10% of initial weight), as desired by obese individuals.[12, 13] We believe that the combination of CMS counseling plus liraglutide plus a 1000-1200 kcal/d portion-controlled diet provides the best opportunity for achieving and maintaining robust losses.[24]

Study Population:

This study is open to men and women with obesity who meet the criteria described below (i.e., inclusion/exclusion). Subjects will be recruited from advertisements in local media outlets (e.g., newspapers, online ads), as well as flyers posted at the University of Pennsylvania. We also will advertise the study to health care providers who work in 23 Penn-owned primary care practices, located throughout greater Philadelphia.

Rationale for study population

The study population has been selected to be consistent with that for which the US FDA approved liraglatide 3.0 (Saxenda) for the treatment of obesity.

Number of subjects to be randomized: 150

Planned number of subjects to be screened: 175 in-person screenings to obtain 150

Planned number of subjects to be treated in run-in period: No run-in period

Planned number of subjects to be randomized to study medication(s): 100

Inclusion Criteria

1. BMI ≥30 kg/m² and ≤55 kg/m²
2. Age ≥ 21 years and ≤ 70 years
3. Eligible female patients will be:

- non-pregnant, evidenced by a negative urine dipstick 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

4. Ability to provide informed consent before any trial-related activities
5. Subjects must:
    - have a primary care provider (PCP) who is responsible for providing routine care
    - have reliable telephone or Internet service to communicate with study staff
    - 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 18 months or more

Exclusion Criteria

1. Pregnant or nursing, or plans to become pregnant in the next 18 months, or not using adequate contraceptive measures
2. Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
3. Uncontrolled hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg)
4. Type 1 diabetes
5. Type 2 diabetes
6. A fasting glucose ≥ 126 mg/dl (on second assessment after first elevated value)
7. 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
8. Clinically significant hepatic or renal disease
9. Thyroid disease, not controlled
10. History of malignancy (except for non-melanoma skin cancer) in past 5 years
11. Current major depressive episode, active suicidal ideation, or history of suicide attempts
12. Psychiatric hospitalization within the past 6 months
13. Self-reported alcohol or substance abuse within the past 12 months, including at-risk drinking (current consumption of ≥ 14 alcoholic drinks per week)
14. Use in past 3 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)
15. Loss of ≥ 10 lb of body weight within the past 3 months
16. History of (or plans for) bariatric surgery
17. Inability to walk 5 blocks comfortably or engage in some other form of aerobic activity (e.g., swimming)
18. Known or suspected allergy to trial medication(s), excipients, or related products
19. Hypersensitivity to liraglutide or any product components
20. The receipt of any investigational drug within 6 months prior to this trial
21. Previous participation in this trial (e.g., randomized and failed to participate)

22. History of pancreatitis
23. Subjects will be included/excluded according to the latest updated US PI.

Withdrawal Criteria

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.

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. These attempts will include at least 1 certified mail receipt. 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

Subjects will be withdrawn according to risk mentioned in the latest updated US PI.

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 liraglutide (e.g., renal failure).
3. A medication is begun that could alter the subject's responses to liraglutide.

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

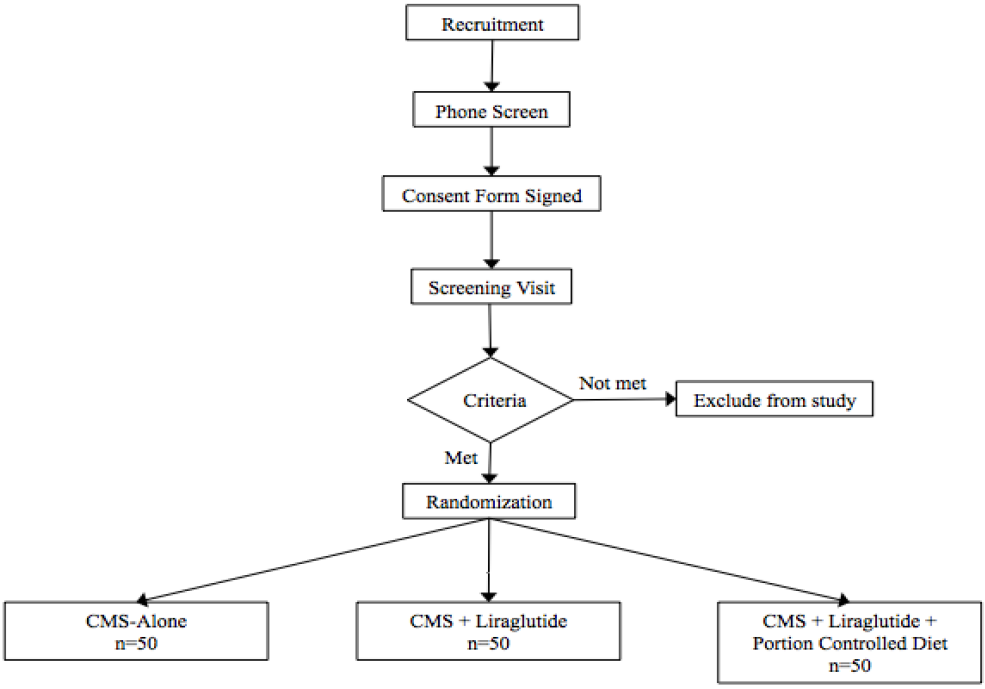
Subject Replacement

Subjects who prematurely discontinue from the study or become ineligible will not be replaced.

Visit Procedures

Figure 1 shows the flow of subjects through randomization. Table 1 presents the schedule of study assessments and treatment visits.

Figure 1. Study Flow Diagram



Screening Procedures

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. Those who appear to meet eligibility criteria and remain interested in the trial will be scheduled for an in-person interview. The Weight and Lifestyle Inventory (WALI),[25] a paper-and-pencil inventory that assesses general eating and lifestyle behaviors, and the Beck Depression Inventory (BDI),[26] will be forwarded to eligible subjects following the phone screen and completed by them prior to their screening/informed consent visit. (All patients and subjects at our Center complete the WALI and BDI to facilitate their initial interview.) 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) and suicidality (including history of suicidal ideation and behavior, as assessed at screening by interview and the Columbia-Suicide Severity Rating Scale).

Subjects who remain interested and pass this portion of the assessment will proceed to meet with the study physician, who will obtain a medical history and conduct a physical examination to determine medical eligibility. Persons who continue to remain eligible will proceed to have an electrocardiogram (EKG) and fasting blood test to determine that final eligibility criteria are met. As detailed below, safety screening labs include a comprehensive metabolic panel (including glucose), lipids, hemoglobin A1c, insulin, hs-CRP and a urine pregnancy test (for females of child-bearing age).

Screening Visit

The following procedures will be completed at the screening visit as discussed above: informed consent; behavioral evaluations; medical history; full physical exam; review of medication; 12-lead EKG; blood draw; weight; height; and sitting blood pressure and pulse rate. For women of childbearing potential, a urine pregnancy test also will be performed. Results of these tests will be reviewed by the study physician to determine whether the subject has any contraindications to weight loss or to the use of liraglutide, as detailed in the inclusion/exclusion criteria.

Participants also will be provided a food record and asked to complete it for 1 week so that they can determine, prior to starting the study, whether they want to keep daily food records for 6 months or more. Keeping such records is a component of lifestyle counseling.Randomization Visit

Participants who meet all eligibility criteria assessed at the screening visit will be scheduled for a randomization screening visit at the Center within 3 weeks of their screening. Approximately 2-3 days before the randomization visit, they will be instructed to complete the self-reported outcomes (described later), either online (using a link e-mailed to them) or using paper-and-pencil questionnaires (for those who prefer this method). Their questionnaires will be reviewed for completeness at the outset of the randomization visit, with any omissions or errors corrected. The participant's weight, blood pressure, and pulse will then be measured, following the methods described later (see Assessment for Efficacy).

Participants will then be randomly assigned to the three interventions in equal numbers (i.e., 1:1:1 ratio). This will be accomplished using a computer-generated algorithm operated by the Center for Weight and Eating Disorders at the University of Pennsylvania. Assignment will be made from randomly varied block sizes (3, 6, or 9).[20]

Following randomization, all participants will have a medical visit with the study physician who will instruct patients in the two medication groups in the use of liraglutide 3.0 (as described later) and provide the first months supply of medication. All

participants also will have an individual lifestyle intervention session (as described in the next session).

Table 1. Schedule of Study Assessments and Lifestyle Intervention Counseling Visits

	Weeks																				
	Screen	R/1	2	3	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	52
	Visit Number																					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
All subjects																						
Informed consent	X																					
Behavioral evaluation	X																					
History and physical	X																					
ECG	X																					
Blood draw	X														X							X
Labs	X														X							X
Self-reported outcomes		X													X							X
Medical visit		X			X		X				X				X				X			X
Lifestyle intervention		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (Weight, BP, HR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMS-Liraglutide Group and Multi-Component Intervention Group Only (CMS + Liraglutide + Meal Replacements)																						
Liraglutide provided		X			X		X		X		X		X		X	X	X	X	X	X	X	
Multi-Component Intervention Only (CMS + Liraglutide + Meal Replacements)																						
Meal replacements					X	X	X	X	X	X	X	X										

Note. R=randomization. Randomization will be followed immediately by week 1 medical visits and lifestyle intervention sessions. Columns shaded in grey indicate principal outcome assessment visists.

Lifestyle Counseling Visits – All Groups

Subjects in all three treatment groups (i.e., CMS-Alone; CMS-Liraglutide; and Multi-Component Intervention) will receive the same program of diet, physical activity, and behavior therapy, as currently recommended (and reimbursed) by the CMS.[2] All study subjects will be provided 14 brief (15 min), face-to-face visits during the first 6 months and 7 visits the second 6 months (total of 21 visits). Lifestyle counseling will be delivered by a nurse practitioner (NP) or by a registered dietitian (RD), the latter working incident to an NP or physician, as required by CMS.[28]

Visits will be scheduled weekly for the first 4 weeks (weeks 1, 2, 3, and 4) and every-other week from weeks 6-24 (weeks 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24) and will be delivered following an abbreviated version of the Diabetes Prevention Program (DPP).[18] (We developed and demonstrated the efficacy of this protocol in our prior POWER-UP study.) From weeks 25-52, subjects will have one brief (15 min) visit per month, as provided by CMS (weeks 28, 32, 36, 40, 44, 48, and 52).

Dietary intake will be prescribed following methods used in DPP[18] and the Look AHEAD study.[29, 30] Subjects in CMS-Alone and CMS-Liraglutide who weigh <250 lb will be prescribed a diet of 1200-1499 kcal/d, comprised of conventional foods, with approximately 15-20% kcal from protein, 20-35% from fat, and the remainder from carbohydrate. (Those who weigh >250 lb will be prescribed 1500-1800 kcal/d.) They will be instructed (for the first 24 weeks) to record their food and calorie intake daily, using paper-and-pencil diaries or on-line trackers (including MyFitnessPal or Lose-It). Subjects will be provided meal plans (which offer breakfast, lunch, and dinner options for the week) that were provided in the DPP[18] and POWER-UP studies.[20] The meal plans are culturally tailored. (As described later, subjects in the Multi-Component Intervention will be prescribed a 1000-1200 portion controlled diet for weeks 4-16 with 2 subsequent weeks of re-feeding, but thereafter will consume the same diet prescribed for subjects in the two other treatment groups.)

The physical activity prescription will be similar to that used in Look AHEAD[30] and POWER-UP.[20] All individuals will be instructed to engage in low-to-moderate intensity physical activity (principally walking or similar aerobic activity) 5 days per week, gradually building to ≥180 minutes per week by week 24. The goal will be increased to ≥225 minutes/week from weeks 25-52, consistent with targets required for the maintenance of lost weight.[31] Subjects will be instructed to record their activity daily and will receive a traditional pedometer (Yamax, Digi-Walker) if they do not own a smart phone with which to track their steps.

The 15 minute intervention visits in the three treatment groups will be conducted using the same format, employed in the POWER-UP study.[20] A subject first will be weighed, in light clothing without shoes. Subject and provider will discuss the weight change from the prior session and whether it meets expectations. They will then review the subject's food and activity records for their prior week to determine the number of days records were kept and the total number of calories consumed and minutes of activity for the

week. Problem solving will be used to address any difficulties encountered. (Records from additional weeks will be reviewed as time allows.) The provider will then review a new topic in weight management, from the treatment protocol, and discuss the subject's accompanying homework assignments for the next session. Subject handouts, which summarize the key learning points and homework assignments for the next session, will be provided for each session. The 14 sessions during the first 24 weeks will provide a full curriculum on behavioral weight control. The 7 sessions from weeks 25-52 will address cardinal behaviors for maintaining lost weight, including regular monitoring of body weight, high levels of physical activity, and relapse prevention.[32] Food and activity records will be collected for the first 24 weeks.

Subjects will be provided print materials, including handouts and food and activity diaries, for those who wish them. However, the 21 DPP lessons[20] will be posted on our Center's web-site, and subjects will have the option of recording their food intake using a variety of apps. Our guiding principle is to tailor the method in which the DPP is delivered to meet the subjects' preferences.

Missed visits will be rescheduled whenever possible. If the subject is unable to complete the visit in person, a telephone call of 15 minute visits may be substituted for the face-to-face meeting. The same meeting format, including a report of the subject's weight, will be followed for phone-delivered sessions as face-to-face meetings. A growing body of evidence indicates that phone-delivered lifestyle counseling is as effective as face-to-face meetings.[33, 34]

Interventionists will include RDs and NPs 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 monthly supervision to deliver the DPP, following the detailed protocols developed for POWER-UP. Interventionists will treat equal numbers of subjects in each of the three treatment groups (to eliminate the possibility of confounding of interventionist and treatment group).

Lifestyle Counseling Visits: The Three Treatment Groups

CMS-Alone. The intervention for subjects assigned to CMS-Alone is described above. There are no additions are alterations to this treatment plan.

CMS-Liraglutide. Participants in this group will receive the identical program of lifestyle modification as those in the CMS-Alone group. The former individuals, however, will be provided liraglutide 3.0 (Saxenda) beginning at week 1. Liraglutide 3.0, a glucagonlike peptide-1 receptor agonist, is a once-daily self-administered, subcutaneous injection.[19] Liraglutide 3.0 will be provided as pre-filled, disposable, personal injectors. Patients will be taught (by the study physician) how to properly perform subcutaneous injections into their abdomen, thigh, or upper arm. In addition, patients will be given an instruction card about how to administer the medication. To reduce the likelihood of gastrointestinal symptoms (e.g., nausea, vomiting), the medication will be initiated at 0.6 mg daily for 1 week, and then increased by 0.6 mg/day in weekly intervals until a dose of 3 mg/day is achieved (please see below for dosing schedule). Patients will be instructed

that if they miss a dose, to resume the once-daily regimen with the next scheduled dose and not to give an extra dose or higher dose. If patients miss more than 3 days, they will be instructed to call the study coordinator/physician who will initiate therapy at 0.6 mg/day to avoid gastrointestinal symptoms. Patients who do not tolerate an increased dose during dose escalation will have a delayed dose escalation by up to 7 days. Study medical staff will help participants develop a medication schedule, based on when and where participants will take the medication each day and how they will remind themselves to do so.

Figure 2. Dosing Schedule for Liraglutide

Lifestyle interventionists working with subjects in this treatment group will briefly review the individual's medication adherence at each visit, determining the number of days liraglutide was used each week and identifying reasons for missed doses. The number of doses of medication taken each week will be tracked. Lifestyle interventionists will not query subjects about side-effects. These will be reported to the research coordinator or the study physician (or NP) at regularly scheduled visits.

Multi-Component Intervention. Subjects in this group will receive the same treatment as those in CMS-Liraglutide, with one exception. Beginning at week 4 (4th brief counseling visit), they will be instructed to consume, for 12 weeks (weeks 4-16), a 1000-1200 kcal/d diet that provides four servings daily of a liquid shake (Health Management Resources – HMR; 160 kcal per shake) and an evening meal comprised of a frozen food entrée (250-300 kcal), with a serving of fruit and a salad. Another serving of fruit will be permitted after dinner, providing a diet of approximately 1000-1200 kcal/day.[16, 17] All HMR products will be provided free of charge; subjects will be responsible for purchasing frozen food entrees and other foods. From weeks 17-18, subjects will be prescribed a re-feeding diet that gradually replaces the consumption of shakes with conventional foods, so that they use of shakes will be fully terminated by week 18. Subjects will record daily the number of meal replacements they use. (Prescription of the portion-controlled diet is expected to increase weight loss by 3 to 5 kg in the first 24 weeks, as compared to consumption of the conventional 1200-1500 kcal/d diet.)[14, 15]

Medical Monitoring Visits

Participants in all three groups also will have brief medical visits (10-15 minutes) with a physician at weeks 1, 4, 8, 16, 24, 40, and 52 (total of 7 visits). These visits are needed for participants in both liraglutide groups to monitor their response to the medication and to check for possible complications of early weight loss. These visits are included for

participants in CMS-Alone to match the intensity of medical care provided the two other groups. Participants in CMS-Alone will be instructed in the relation of excess weight to health and review results of their laboratory tests. At each medical visit, participant's weight and vital signs will be measured and their response to the medication will be assessed. Study subjects will be asked whether there have been any changes in their health or medications. For all non-study-related medical events, participants will be referred to their own primary care providers. Participants also will be asked about their mood or any thoughts of harming themselves, as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS).[27] In the event of reports of suicidal ideation or disturbances in mood, participants will be referred to the study's psychologist or psychiatrist for further evaluation, as appropriate.

Assessments for Efficacy

Participants will attend 3 major outcome assessment visits, conducted at randomization, week 24 and week 52 (see Table 1). All outcomes described below will be measured on these three occasions.

Primary Efficacy Measure

The primary outcome is % reduction in initial body weight, as measured from randomization to week 52. Secondary outcomes include the proportion of participants who at week 52 lose $\geq$5%, $\geq$10%, and $\geq$15% of initial weight, as well as % reduction in weight at week 24 and the proportion of participants who meet the three categorical weight losses at this time. Body weight will be measured on a digital scale (to the nearest 0.1 kg) with participants dressed in light clothing, without shoes. Two measurements will be taken on each occasion and averaged. Weight will be measured by an assessor masked to participants' treatment condition. (Body weight also will be measured at each lifestyle counseling visit but the assessor will not be masked to treatment condition on these occasions.)

Secondary Efficacy Measures

The secondary efficacy measures include changes in cardiovascular disease (CVD) risk factors (i.e, blood pressure, triglycerides, LDL and HDL cholesterol, C reactive protein, and waist circumference), glycemic control (i.e., fasting blood sugar, HbA1c, insulin, and HOMA), mood (PHQ-9), quality of life (i.e, SF-36 and IWQOL-Lite), eating behavior (i.e., Eating Inventory, Eating Disorder Examination-Questionnaire, and Yale Food Addiction Scale), appetite (i.e., visual analogue scales), sleep (i.e., Pittsburgh Sleep Quality Index), and satisfaction with weight loss.

Cardiometabolic risk factors will be assessed at screening and weeks 24 and 52, following methods described previously.[4, 20] (Screening values will be used as the randomization value, given that they will be obtained within 3 weeks of participants being randomized.)

Fasting blood samples (i.e., following an 8-hr overnight fast) will be drawn by study personnel on each occasion and assayed for comprehensive metabolic panel (including glucose), lipids (e.g., triglycerides, total-, HDL-, and LDL-cholesterol), hemoglobin A1c, insulin, and hs-CRP. Insulin sensitivity will be calculated using HOMA. (Blood samples will be analyzed by Quest Diagnostics.)

Blood pressure and pulse will be measured at each outcome assessment using an automated monitor (Dinamap, model 9300).[4, 20] Two readings will be taken on each occasion (at 1-minute intervals), after participants have been seated for at least 5 minutes. (Blood pressure and pulse also will be measured at all medical visits, as well as at lifestyle counseling visits.)

Waist circumference will be measured (following methods described previously) to the nearest 0.1 cm on the same three occasions.[35] Two waist measurements will be obtained at each assessment visit and averaged.

Mood, quality of life, eating behavior, and appetite. Mood will be assessed on the same schedule as the primary outcome using the PHQ-9.[36] Quality of life will be assessed on the same schedule as the primary outcome using SF-36 [37] and IWQOL-Lite.[38] Cognitive restraint, disinhibition, and hunger will be evaluated at the same time, using the Eating Inventory (EI)[39] and visual analogue scales[40], and binge eating will be assessed by the Eating Disorder Examination-Questionnaire (EDE-Q).[41] Food addiction will be measured using the Yale Food Addiction Scale.[42] Satisfaction with weight loss will be assessed following methods used by Foster and Wadden.

Assessments for Safety

Safety endpoints include physical examination, adverse events (AEs), standard laboratory tests, and mental health/suicidal behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS). As detailed above, participants in all three groups also will have brief medical visits (10-15 minutes) with a physician at weeks 1, 4, 8, 16, 24, 40, and 52 (total of 7 visits). These visits are needed for participants in both liraglutide groups to monitor their response to the medication and to check for possible complications of early weight loss. At each medical visit, participant's response to the medication will be assessed. Study subjects will be asked whether there has been any change in their health or medications. They also will be asked about their mood or any thoughts of harming themselves, as determined by the C-SSRS. In the event of adverse mental health events, participants will be referred to the study's psychologist or psychiatrist for further evaluation, if required. For all non-study-related medical events, participants will be referred to their own primary care provider.

Participants will have fasting blood draws (comprehensive metabolic panel, lipids, hemoglobin A1c, insulin, hs-CRP) at screening, and weeks 24 and 52. Vital signs (blood pressure and pulse) and weights will be measured at screening and weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40, 44, 48, and 52.

Subject Compliance

We will measure subject's medication adherence using injection counts from visual inspection of the dose counter taken from subjects' injection pens. Patients will be instructed to bring the pen to each session, and we will record missed doses and problem solve with patients if they are missing doses. Patients will be instructed to keep a medication diary, as part of their food and activity monitoring.

STATISTICAL CONSIDERATIONS:

Sample Size Calculation

At week 52, subjects assigned to CMS-Alone are predicted to lose 5% (SD=5.0) of initial weight, while those in CMS-Liraglutide will lose 9.5% (SD=7.0), and those assigned to the Multi-Component Intervention will lose 14% (SD=8.0). The predicted effect for CMS-Alone is based on the results of the Hopkins POWER study in which 15 brief (15-20 min) individual telephone calls with a trained interventionist induced a mean loss of 6.1 kg in 24 weeks (equal to 5% of initial weight). The effect for CMS-Liraglutide is estimated at 9.5%, with the expectation that liriglutide 3.0 mg/d will increase weight loss above placebo by 4.5% (a conservative estimate based on results of the three SCALE studies summarized in the Saxenda PI).[19] The 14% reduction in initial weight for the Multi-Component Intervention is based on our prior results with the combination of an intensive lifestyle intervention plus sibutramine plus a 1000-1200 kcal/d diet.[9]

Using a sample size equation for longitudinal clustered samples, a randomization sample of 50 subjects in CMS-Alone, 50 in CMS-Liraglutide, and 50 in the Multi-Component Intervention provides >80% power to detect the two primary contrasts to be statistically significant at the Holm's[43] adjusted alpha levels noted above. This estimate allows for 20% attrition during the 52-week trial, resulting in approximately 40 treatment completers per group. (The 20% attrition level is conservative; it is higher than what we observe in most of our trials conducted at Penn.) The ITT longitudinal statistical design will further improve power by allowing the inclusion of available data for non-completers and the adjustment of possible variance reducing baseline covariates. All secondary analyses will be considered exploratory and evaluated at the alpha = 0.05 level. The power analysis was conducted using PASS 11.

Statistical Methods

Preliminary Analyses

All data will first be assessed by the data management staff for missing data and out-of-range values with basic statistical procedures such as univariate statistics (i.e., means, standard deviations, ranges, frequencies, proportions, percentiles) and graphs, such as histograms, box and whisker plots, scatter plots and Q-Q plots. In addition, plots will be produced of individual and average trajectories of all repeated measures over time according to assigned treatment. All questions of data quality and integrity will be

investigated before any statistical modeling is conducted.

Next, a preliminary analysis of all outcome and baseline demographic variables will be performed to test for differences in baseline measures between the randomized groups. The test of the adequacy of randomization will consist of tests of differences between the treatment conditions to see if the baseline variables are equally distributed between them. These baseline comparisons will be based on: t-tests or Wilcoxon rank sum tests for continuous variables, depending on the symmetry of the distributions; on Chi-square, Fisher's Exact or logistic regression for binary or ordinal variables; and on Poisson log-linear regression for count data. If imbalances are found at baseline, then the relevant variables will be treated as confounders in the post study analyses.

The primary analysis will test the hypothesis that subjects randomly assigned to CMS-Liraglutide and the Multi-Component Intervention will lose a significantly greater percentage of initial weight at week 52 than will those assigned to CMS-Alone. A linear mixed model will be fit using the mixed procedure in the statistical software package SAS, version 9.3. An intention-to-treat (ITT) analysis (including all randomized subjects) will fit an unstructured covariance matrix to adjust for the repeated measures data clustered with the individual subject. In addition, these models will contain the following fixed effects: main effect for change from baseline to each follow-up visit (weeks 24 and 52); group (3 treatment conditions); and the interaction between the visit and group.

The study's primary outcome will consist of two pairwise comparisons: 1) 52 week % reduction in initial weight in CMS-Alone compared with CMS-Liraglutide; and 2) 52-week % reduction in initial weight in CMS-Alone compared with the Multi-Intervention. Based on the Holm's procedure, which adjusts for multiple comparisons, 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.[44]

Comparison of CMS-Liraglutide and the Multi-Component Intervention is considered a secondary outcome and will be examined with alpha equal to 0.05.

All randomized participants will be included in the primary intention-to-treat (ITT) analysis. A per protocol analysis will be conducted that includes only those participants who provide a measurement of body weight at week 52 (with a window of $\pm$4 weeks). All randomized participants will be included in the safety analysis.

Secondary Analyses

Similar analytic strategies will be employed for all other continuous secondary efficacy endpoints, as well as for binary (dichotomous outcomes; i.e., percentage of participants who achieve different criterion weight losses). For the logistic model, differences will be presented as odds ratios with confidence intervals; for linear model, the least squares means and standard errors will be presented with confidence intervals. Analyses of all secondary outcomes will be considered exploratory, with all pairwise-comparisons of the three intervention groups examined with alpha equal to 0.05.

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 participants 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.[45] 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.

Weight loss data also will be analyzed using a per protocol analysis that, for liraglutide-treated participants, includes only those who were able to tolerate and adhered to the full dose of liraglutide 3.0 mg.

Interim Analysis

No interim analyses are planned (in order to maintain full power for the end-of-study comparisons).

Explorative Statistical Analysis for Pharmacogenetics and Biomarkers

No explorative statistical analysis for pharmacogenetics and biomarkers will be performed.

Data Handling and Record Keeping:

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:

- Protected health information (PHI) 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 research subjects to revoke their authorization for use of their PHI
- View of PHI will be limited to individuals at the University of Pennsylvania directly involved in the study. The company donating the study product will not have access to 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 who have revoked authorization to collect or use PHI, attempts will 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.

Ethics:

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 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, gender 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.

Study Schedule:

Table 2. Study Timeline

	2016				2017				2018			
Study start	5/1											
Recruitment												
First patient screening visit	6/1											
Enrollment/randomization	12-15 subjects/month											
Last patient first visit					5/1				5/1			
Data collection	6/1								5/1			
Data analysis/manuscripts										10/30		
Final study reports										10/30		

Study Drugs and Materials:

Subjects assigned to liraglutide will need 365 doses (12 pens) of study medication. Subjects will be provided with a 30-day supply of medication (1 pen) on 12 occasions. We will assign 100 subjects to liraglutide and, thus, will need a total of 120 pens of liraglutide.

Study Medication

The study medication is liraglutide (i.e., Saxenda). It will be initiated at 0.6 mg subcutaneously, daily for 1 week, and increase by 0.6 mg/day in weekly intervals until a dose of 3 mg/day is achieved. The pen delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg (6 mg/mL, 3mL).

Packaging and Labelling of Study Medication

The medication will be provided by Novo Nordisk as ready-to-use, pre-filled, multi-dose pens by Novo Nordisk in a subject box.
Study drug will be shipped to the Center for Weight and Eating Disordersat the University of Pennsylvania (attention Dr. Tom Wadden) for labeling and packaging. The study drug supplies will be labeled appropriate to their use. The label for the study drug will contain at a minimum:

- Protocol number
- Kit identification number from the randomization scheme
- Instructions for use
- Study drug name

Storage and Drug Accountability of Study Medication

The medication will be refrigerated (36-46°F) (the temperature will be checked daily.) After first use, the subject may store the medication at room temperature (59-86°F) or refrigerate (36-46°F). The injection pen expires 30 days after first use. The sponsor-investigator will ensure the availability of proper storage conditions and record and evaluate the temperature. No trial medication(s) will be dispensed to any person not enrolled in the study. Unused medication(s) will be stored separately from used trial medication(s). Subjects will be instructed to inspect the medication visually for particulate matter and discoloration prior to administration.

We will maintain adequate drug inventory and security at all times. Upon receipt of the study drug, the Center for Weight and Eating Disorders at Penn will perform an inventory of the shipment, comparing the shipment inventory to actual study drug received, and complete and sign an inventory log. The study investigators will immediately notify Novo Nordisk (or its designee) or the drug distribution contractor of any damaged or unusable study drug that the center receives, and document in the inventory log any damaged or unusable study drug. We will request that additional study drug be shipped as needed.

The drug supplies will be kept in a secured enclosure with limited access at the Center for Weight and Eating Disorders, where it will be received and dispensed to subjects. The investigator will take appropriate precautions to prevent theft or diversion of the study drug.

At the conclusion of the study, a final inventory of study drug shipped, dispensed, and remaining at the Center for Weight and Eating Disorders will be performed by the investigator. This reconciliation will be entered on the drug accountability log. The investigator will return all unused drug to Novo Nordisk or its designee, unless alternative arrangements for drug disposal are authorized. No study drug will be retained when the study is completed; all study drugs will be returned to Novo Nordisk or its designee for destruction.

Randomization and Blinding

Dr. Jena Shaw from the Center for Weight and Eating Disorders will generate the randomization code. The randomization will be generated using a randomization scheme of CMS-Alone to CMS-Liraglutide to Multi-Component Intervention. The first subject to meet the treatment criteria will be assigned the first number in the sequence; each subsequent subject to meet treatment criteria will be assigned the next number in the sequence. This is an open-labelled randomized trial.

Breaking of Blinded Codes

Not applicable

Concomitant Illnesses and Medications:

At trial entry (i.e., the screening visit), we will record details of any concomitant illness (i.e., any illness that is present at the start of the trial) that is present and concomitant medication (i.e., any medication other than the trial product(s) that is taken during the trial, including the screening and run-in periods) in each patient's record. The information collected for each concomitant medication will include the start date, stop date or continuing, and indication. For each concomitant illness, we will record the date of onset, date of resolution or continuing. Any changes in concomitant medication use will be recorded at each visit. If the change influences the subject's eligibility to continue in the trial, the Sponsor will be informed.

Adverse Events:

At each contact with subjects, study personnel will be responsive to reports of adverse events with specific questioning and, as outlined in the procedures section, by physical examination. The investigator will be report all adverse events including serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSARs), serious adverse drug reactions (SADRs) (as defined below) to the Data Safety and Monitoring Board established for the trial, and to the Penn IRB. 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). Information on study name, patient identification, event (i.e., diagnosis, causality), drug, and reporter identification (e.g., name) will be collected and recorded in the source document (as detailed below). All serious adverse events will be reported to the IRB within 24 hours. The investigator will report to Novo Nordisk all SAEs, SUSARs, and SADRs at the same time such events are reported to regulatory authorities or within 15 days from the investigator becoming aware of such adverse events, whichever comes first.

The PI and his investigative team acknowledge the definition of adverse events (AEs), serious adverse events (SAEs), and other untoward occurences as spelled out below.

Adverse Event (AE):
An AE is any untoward medical occurrence in a patient or clinical investigation subject administered/using a product and which does not necessarily have to have a causal relationship with this treatment. An Adverse Event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product.

Clinical Laboratory Adverse Event:
A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management, (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

Serious Adverse Event (SAE):
A serious AE is an experience that at any dose results in any of the following:
• Death
• A life-threatening* experience
• In-patient hospitalisation or prolongation of existing hospitalization
• A persistent or significant disability/incapacity
• A congenital anomaly/birth defect
• Suspicion of transmission of infectious agents
• Important medical events that may not result in death, be life-threatening*, or require hospitalisation may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

*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.

Suspected Unexpected Serious Adverse Reaction (SUSAR): A SUSAR is an SAE which is unexpected and regarding as possibly or probably related to the trial/study product by the investigator.

Serious Adverse Drug Reaction (SADR):

An adverse drug reaction (ADR) is an adverse event for which a causal relationship (Possible/Probable relation) between the study drug and the occurrence of the event is suspected. The ADR should be classified as **serious** if it meets one or more of the seriousness criteria.

Medical Events of Special Interest (MESI): A MESI is (1) a medication error (e.g. wrong drug administration or wrong route of administration) or (2) a suspected transmission of an infectious agent via the product

Non-Serious Adverse Event:
A non-serious AE is any AE which does not fulfil the definition of an SAE.

Severity Assessment Definitions:
• Mild: Transient symptoms, no interference with the subject's daily activities
• Moderate: Marked symptoms, moderate interference with the subject's daily activities
• Severe: Considerable interference with the subject's daily activities, unacceptable

Relationship to study medication Assessment Definitions:
• 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

The US PI will be used to evaluate all unexpected events and adverse reactions.

Outcome Categories and Definitions:
• Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
• Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
• Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
• Not recovered
• Fatal
• Unknown

Collection, Recording and Reporting 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 posttreatment follow-up period as stated in the protocol.

Follow-up of Adverse Events
During and following subjects' participation in the study, the investigator and institution will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. (Note: This

section of the protocol will be written in consultation with Penn's IRB, Office of Research Services, and Office of Legal Affairs. It will be addressed pending approval of the scientific aspects of the study.)

Pregnancy

Study subjects will be instructed to notify the investigator immediately if they become pregnant. The investigator will report to Novo Nordisk any pregnancy occurring during the trial period. 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.

Precautions/Over-dosage

In case of suspected overdose, subjects will be instructed to call their healthcare provider immediately, as excessive intake of Saxenda may cause severe nausea and vomiting.

Liability and Subject Insurance:

Liability and subject insurance will be discussed during the second phase of the application, in consultation with Penn's Office of Research Services and Legal Affairs.

Evaluability of Subjects:

Participants will be excluded from data analysis in the event of pregnancy, amputation, bariatric surgery, or death. Additional criteria associated with subject censorship will be considered prior to initiating recruitment.

Premature Termination of Study:

We believe that it is highly unlikely that the study will be terminated prematurely, given the safety of the intervention and its expected effects. Termination would be considered, however, in view of:

- Unacceptable safety concerns of the study medication
- The benefits observed do not ethically permit the trial to continue

Publication Plan:

We will register the study with a publicly assessable database such as clinicaltrials.gov. An initial report of the findings will be presented at an annual scientific meeting (e.g., American Diabetes Association, The Obesity Society, The American Heart Association). We plan to publish the study results approximately 6 months after study completion.

The report of the primary outcome will be submitted to the New England Journal of Medicine. Secondary papers likely will be submitted to Obesity, International Journal of Obesity, or primary care journals.

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Addendum to the Protocol in Order to Study the Efficacy of Liraglutiude 3.0 mg/d Combined with Phentermine 15 mg/d to Increase Weight Loss in a 12-Week Placebo-Controlled Trial, Following Completion of the Original 1-Year Study

Table of Contents

SUMMARY OF THE PROPOSED PROTOCOL ADDENDUM

The above protocol describes a 52-week, open-label, three arm trial titled "Combining lifestyle modification and liraglutide to improve weight loss and health outcomes." The study, with a total sample of 150 participants, compares changes in weight and other health outcomes in individuals randomly assigned to: 1) brief lifestyle counseling alone, as recommended by the Centers for Medicare and Medicaid Services (CMS-Alone); 2) CMS counseling plus liraglutide 3.0 mg/d (CMS-Liraglutide); or 3) the combination of CMS counseling, liraglutide 3.0 mg/d, and the provision of a 1000-12000 meal replacement diet for the first 12 weeks (i.e., Multi-Component Intervention).

The study's primary hypothesis is that participants assigned to the Multi-Component Intervention will lose significantly more weight at 1 year than those assigned to CMS-Liraglutide (14.0% vs 9.5%), who, in turn, will lose significantly more than those assigned to CMS-Alone (9.5% vs 5.0%).

The Addendum described below requests no changes to the present 1-year protocol.

Instead, it proposes a 20-week extension of the present 1-year trial for participants assigned to the CMS-Liraglutide and the Multi-Component Intervention groups. During the first 12 weeks of the extension, we will test, in a randomized, placebo-controlled trial, the hypothesis that the addition of phentermine 15 mg/d to liraglutide 3.0 mg/d will produce significantly greater weight loss at week 12 than will the combination of placebo plus liraglutide 3.0 mg/d. We hypothesize that the difference between groups will be approximately 3.5% of initial weight, as measured from randomization. Patients and their practitioners would welcome this additional weight loss, if the medications together were shown to have an acceptable safety profile, which we believe they will.

At the end of week 12 (post-randomization), phentermine and placebo will be terminated, but both groups will remain on liraglutide 3.0 mg/d until week 20. We wish to observe, from weeks 12 to 20, the change in body weight that occurs with the termination of phentermine 15 mg/d. At week 20, liraglutide also will be terminated in both groups of participants. At week 24 (post-randomization), all participants will have a final assessment with a physician or nurse practitioner to determine participants' health status.

All participants from the CMS-Liraglutide and Multi-Component Intervention groups who complete the original 1-year randomized trial – and who have remained on liraglutide 3.0 mg/d - will be invited to enroll in the 20-week extension study, immediately upon completing the prior 1-year trial. (Participants in the CMS-Alone group will not be eligible to receive medication but they will be offered continued brief-monthly lifestyle counseling sessions, similar to those provided in the original 1-year trial.) Participants eligible for the 20-week medication-extension study will sign a new, separate consent form, apprising them of the potential risks and benefits of treatment with liraglutide plus phentermine (or placebo). They all will complete a brief history and physical examination, including an EKG, prior to randomization and will be determined to have acceptable blood pressure and pulse rate. (Participants in the CMS-Alone group who wish to continue in the 6-month extension study will sign a separate consent form

and will not be required to undergo additional safety assessment/monitoring, beyond the assessment conducted at the end of the original 1-year trial.

All study participants from the original CMS-Liraglutide and Multi-Component Intervention groups will be prescribed liraglutide 3.0 mg/d for an additional 20 weeks. In addition, they will be stratified into two groups, based on whether they have lost $\geq$10% of initial weight at the end of the 1-year. They will be randomly assigned from these blocks to liraglutide 3.0 mg/d plus phentermine 15 mg/d or liraglutide 3.0 plus placebo. Phentermine will be purchased by the principal investigator (using discretionary funds, not provided by Novo Nordisk) and will be prepared in matching drug and placebo capsules by Dr. Ken Rockwell, director of Penn's Investigational Drug Service. Dr. Rockwell will be responsible for distributing phentermine and placebo and for randomizing participants to treatment. Phentermine will be provided as 8.0mg/d during the first 2 weeks of the extension study and increased to 15 mg/d at week 3. Phentermine (or placebo) will be down-titrated (back to 8.0 mg/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 Dr. Rockwell, in response to notification from the principal investigator (or study co-investigators) of patients' complaints of symptoms. (With Dr. Rockwell, we successfully used this titration method in a prior randomized placebo-controlled trial of sibutramine for weight loss.[46]) Participants in whom phentermine (or placebo) is terminated will continue to receive liraglutide 3.0 mg, in an open-label manner, as they have for the prior 1-year trial.

All participants in the randomized, 12-week extension study will meet with a physician or nurse practitioner at randomization (week 0) and at weeks 2, 4, 8 and 12. On each occasion they will review patients' blood pressure and pulse, assess suicidal ideation, and record and respond to reports of changes in physical health. As during the 1-year prior trial, brief lifestyle counseling (15 min) will provided at each visit (except week 2) by the physician or nurse practitioner or by a registered dietitian or behavioral psychologist, working incident to the two first providers.

At the conclusion of the 12-week randomized extension, all participants will stop taking phentermine 15 mg/d (or placebo). They will continue to receive liraglutide 3.0 mg/d for an additional 8 weeks (week 20). They will meet at weeks 16 and 20 with a physician or nurse practitioner who will review their blood pressure and pulse, assess suicidal ideation, and record and respond to reports of changes in physical health. Brief lifestyle counseling visits (15 min) will be provided at each visit as described previously. At week 20, liraglutide 3.0 mg/d will be terminated in all patients, who will have a final assessment with a physician or nurse practitioner at week 24 to determine

We anticipate that 35 (of 50) participants from the original CMS-Liraglutide group and 35 (of 50) from the Multi-Component Intervention will be eligible to participate in the extension study and will elect to do so. We anticipate that 32 participants in each group will complete the 12-week randomized, extension trial and that those who receive liraglutide 3.0 mg/d plus phentermine 15.0 mg/d will lose, from randomization to week 12, 3.5±3.5% (of randomization weight), compared with 0.0±0.5% for those assigned to

liraglutide plus placebo. With the expected sample size, we will have 80% power to detect this difference, using a two-tailed p value of p = 0.05. (We also will examine total weight loss in the two groups, as measured from the original randomization weight [from the preceding 1-year trial], but this is not a primary outcome of the study.)

The finding that phentermine 15.0 mg/d produces additional weight loss when added to liraglutide after 1 year's use of the latter medication would be welcomed news to patients and their practitioner. Patients wish to lose more weight than current treatments induce, and they particularly seek methods to resume weight loss after hitting a prolonged plateau. The proposed pilot study provides a highly efficient method for both the investigative team to determine whether the combination of liraglutide 3.0 mg/d plus phentermine 15.0 mg/d provides such benefit, or at least a signal of such benefit. The 8-week observational follow-up period, from weeks 12-20, in which all participants will continue to receive liraglutide 3.0 mg/d, but not phentermine (or placebo), will provide preliminary evidence concerning the maintenance of weight loss (or possible weight regain) following termination of phentermine 15.0 mg/d.

The sections that follow parallel the original sections of the protocol for the 1-year trial described above. Additional information is added to each section, as required, to describe the 12-week extension study and any modifications to the original methods needed for the 12-week trial (e.g., change in eligibility criteria). With each section, in the absence of the need for additional material to explain the extension study, the reader is referred back to the original sections presented for the 1-year trial.

BACKGROUND AND SIGNIFICANCE

The perils of obesity and benefits of weight loss are well documented, including in the original Background and Significance section of this protocol. Liraglutide 3.0 mg/d, a glucagon-like peptide-1 (GLP-1) agonist, has been shown to induce clinically significant, long-term weight loss of approximately 8.0% of initial body weight, when combined with a moderate-intensity program of lifestyle modification. Larger weight losses, as desired by patients, potentially may be obtained by combining liraglude 3.0 with a low-calorie meal replacement diet (i.e., 1000-1200 kcal/d), delivered during a preliminary run-in period.[47] Larger weight losses also may be obtained by combining the medication with intensive behavior therapy (IBT), providing 14 or more brief, individual counseling sessions in 6 months, as currently being tested in two randomized clinical trials supported by Novo Nordisk. A third option to increase weight loss with liraglutide 3.0 mg/d is to combine it with another weight loss medication. Phentermine hydrochloride (15.0 mg/d) is one such option.

Phentermine, as monotherapy, is the most widely used weight loss medication in the U.S. It was approved by the Food and Drug Administration (FDA) in 1959 for "short-term" use, commonly interpreted as 12 or fewer weeks.[48] Phentermine is a sympathomimetic amine that is thought to reduce food intake by increasing norepinephrine and possibly serotonin levels in the hypothalamus. When provided as 8.0 or 15.0 mg/d, the medication induces weight loss of approximately 4.0 kg (or 4.0%) greater than placebo at 12 to 28

weeks.[48] Phentermine also increases weight loss when combined with other medications known to affect body weight. The FDA-approved combination of phentermine and topirimate, prescribed at 15.0 mg/d and 92 mg/d, respectively, produced a mean loss of 11.6% of initial weight at 28 weeks, compared with 7.4% for phentermine alone and 8.8% for topirimate alone (using the same doses for monotherapy. Placebo produced a loss of 2.3%.[49]

A recent 12-week pilot study showed that the addition of 15 mg/d of phentermine to lorcaserin (10 mg/BID) increased weight loss from 3.3±3.4% to 6.7±5.4%. The addition of 30 mg/d of phentermine (to lorcaserin) increased the loss to only 7.2±4.6%, but substantially increased adverse events as compared with the 15 mg dose of phentermine. This combination therapy had a relatively favorable side-effect profile, particularly with the 15 mg dose of phentermine. Systolic and diastolic pressure fell by 3.3 and 1.4 mm Hg, respectively, with lorcaserin/phentermine 15 mg/d, compared with reductions of 5.5 and 2.5, respectively, in the lorcaserin-alone group. Pusle rate increased by 1.1 beats per minute (BPM) in the combination group, compared with a fall of 1.9 BPM in the lorcaserin group. Aronne et al observed similar, generally favorable changes in blood pressure and pulse at 28 weeks with phentermine 15.0 mg.[49]

OBJECTIVES

Primary Objective

To compare the 12-week mean percentage reduction in weight in participants, who following completion of the original 1-year trial, are randomly assigned to receive liraglutide 3.0 mg/d combined with phentermine 15 mg/d versus liraglutide 3.0 mg/d combined with placebo.

Co-Primary Objective

To assess the safety of liraglutide 3.0 mg/d combined with phentermine 15 mg/d, as well as liraglutide 3.0 alone, as determined by assessment of standard blood chemistries (measured throughtout the 1-year trial), measurement of blood pressure and pulse, and recording of adverse events (AEs) reported by participants. AEs of special interest, previously reported with phentermine 15 mg/d, include dry mouth, constipation, nausea, and insomnia.

Secondary Objective

To compare the two medication regimens in the proportion of participants who lose 5% or more or 10% or more of initial weight from randomization to week 12.

To compare differences between the two groups in 12-week changes in secondary endpoints, described in the next section.

To compare the total mean weight loss achieved by participants in the two medication regimens, as determined from their original randomization weight at the start of the original 1-year trial.

To examine the change in body weight (in the two groups) from weeks 12 to 20 when participants will have terminated phentermine (or placebo) but remained on liraglutide 3.0 mg/d. This is an observational, exploratory outcome.

RESEARCH DESIGN AND METHODS:

Study Hypotheses:

Primary aim 1: To compare the 12-week mean percentage reduction in weight in participants, who following completion of the original 1-year trial, are randomly assigned to receive liraglutide 3.0 mg/d combined with phentermine 15 mg/d versus liraglutide 3.0 mg/d combined with placebo.

H_1: The combination of liraglutide 3.0 mg and phentermine 15 mg/d will produce significantly greater mean weight loss at 12 weeks post-randomiization than will liraglutide 3.0 mg combined with placebo (with expected mean losses of 3.5% and 0.0%, respectively).

Co-primary aim 1: To assess the safety of liraglutide 3.0 mg combined with phentermine 15 mg/d, as well as that of liraglutide 3.0 mg combined with placebo, during the 12 week placebo-controlled trial. Standard assessments of safety will be conducted, as described in the original protocol for the 1-year trial.

Endpoints:

Primary

The primary endpoint is change in body weight (i.e., % reduction in randomization weight), as measured from randomization (week 0) to week 12.

Secondary

Secondary endpoints include the proportion of subjects who lose $\geq$ 5% or $\geq$ 10% of initial weight from randomization to week 12, as well as changes from randomization to week 12 in cardiovascular disease (CVD) risk factors (i.e, blood pressure, triglycerides, LDL and HDL cholesterol, and waist circumference), glycemic control (i.e., fasting blood sugar), mood (PHQ-9), quality of life (i.e, SF-36 and IWQOL-Lite), eating behavior (i.e., Eating Inventory, Eating Disorder Examination-Questionnaire, and Yale Food Addiction Scale), appetite (i.e., visual analogue scales), sleep (i.e., Pittsburgh Sleep Quality Index), and weight loss satisfaction. (All of these measures were administered in the original 1-year trial.)

A secondary analysis will examine differences between the two randomized groups in changes in weight and other outcomes as measured from participants' original randomization values, when starting the original 1-year trial.

Study type:

This is a 12-week, single center, randomized placebo-controlled, parallel group design trial. Participants and investigators will be masked to participants' assignment to phentermine 15 mg/d versus placebo. Participants in both groups will receive liraglutide in an open-label manner.

We anticipate that 35 (of 50) participants from the original CMS-Liraglutide group and 35 (of 50) from the Multi-Component Intervention will be eligible to participate in the extension study and will elect to do so. We anticipate that 32 participants in each group will complete the 12-week extension study and that those who receive liraglutide 3.0 mg plus phentermine 15.0 mg/d will lose, from randomization to week 12, 3.5$\pm$3.5% of initial weight, compared with 0.0$\pm$0.5% for those assigned to liraglutide plus placebo.

All participants in the extension study will meet with a physician or nurse practitioner at randomization (week 0) and at weeks 2, 4, 8 and 12. On each occasion they will review patients' blood pressure and pulse, assess suicidal ideation, and record and respond appropriately to reports of changes in physical health. As during the 1-year prior trial, brief lifestyle counseling (15 min) will provided at monthly visits (excluding week 2) by the physician or nurse practitioner or by a registered dietitian or behavioral psychologist, working under their supervision. The lifestyle intervention will be the same as that provided during the last 6 months of both the CMS-Liraglutide and Multi-Component interventions.

Following the 12-week randomized trial, phentermine (or placebo) will be terminated, and all participants will continue to receive liraglutide 3.0 mg/d for an additional 8 weeks (i.e., weeks 12-20) and have lifestyle counseling and medical assessments at weeks 16 and 20. Liraglutide 3.0 mg/d will be terminated at week 20, and participants will have a final safety assessment at week 24.

Rationale for Study Design

The proposed study will provide only 12 weeks of treatment with the combination of liraglutide 3.0 mg/d and phentermine 15 mg/d. The limited duration is based on phentermine's only being approved by the FDA for short-term use, commonly interpreted as 12 weeks. Our adherence to this duration of use should limit participants' exposure to any unknown (and unexpected) risks. We believe, however, that the 12-week duration will be sufficiently long to detect a signal that the combination is effective in increasing weight loss and that it is generally safe. The trial will provide valuable pilot data that could form the basis of larger study, capable of fully assessing the long-term safety and efficacy of the combination

Our study does not include a comparison of liraglutide 3.0 mg alone to phentermine 15 mg alone, because we are using liraglutide as a background treatment for all participants to determine whether the addition of phentermine 15 mg/d increases weight loss, as compared to the use of liraglutide alone. In this regard, the study contains no comparative assessments of the benefits of liraglutide 3.0 mg vs phentermine 15 mg alone, in the same manner that the recent lorcaserin plus phentermine study did not directly compare the efficacy of the two medications.[50]

Study Population:

All participants from the original CMS-Liraglutide and Multi-Component Intervention groups who complete the 1-year trial – and have remained on liraglutide 3.0 mg/d - will be potentially eligible to enroll in the 12-week extension study, immediately upon completing the prior 1-year trial. (Participants in the CMS-Alone group will not be eligible to participate in the randomized trial. However, they will be offered 6 additional, monthly brief lifestyle counseling visits, through week 20 of the extension study.) Participants eligible for the extension study will sign a new consent form, apprising them of the potential risks and benefits of treatment with liraglutide plus phentermine (or placebo). Prior to randomization, they all will complete a brief history and physical examination, including an EKG, and will be determined to have acceptable blood pressure and pulse, using the same criteria employed in the original study. (Participants in the CMS-Alone group also will complete a new consent form but will not be required to undergo additional safety assessments or monitoring, past the assessment conducted at the 1-year visit in the original study.)

This study is open to men and women with obesity who meet the criteria described in the original protocol (i.e., inclusion/exclusion).

Rationale for study population

The study population has been selected to be consistent with those for which the US FDA approved liraglatide 3.0 mg/d and approved phentermine 15.0 mg/d.

Number of subjects to be randomized: 70 (from the 1-year randomized trial that all participants will have completed)

Planned number of subjects to be screened: approximately 85-90 (i.e., all participants in the two liraglutide treated conditions who complete the 1-year trial – and remain on liraglutide 3.0 - will be invited to participate in the 12-week extension study).

Planned number of subjects to be treated in run-in period: No run-in period

Planned number of subjects to be randomized to study medication(s): 35 randomized to liraglutide plus phentermine and 35 to liraglutide plus placebo.

Inclusion Criteria

Inclusion criteria are those described for the original 1-year trial (enumerated above). The principal exception from these criteria is that participants will only be required to have a BMI $\geq$ 27 kg/m^2, with or without co-morbidities, to be eligible to participate in the extension study. All participants will have met BMI inclusion criteria when they initiated the use of liraglutide and now will use it, potentially with phentermine 15 mg/d, to facilitate to the maintenance of lost weight. (Liraglutide is approved for chronic weight management, including following successful weight loss.) We do not wish to enroll participants with a BMI < 27 kg/m^2 because of the possibility that they could reduce substantially below a BMI of 24.9 kg/m^2, the upper limit of "normal" weight.

Exclusion Criteria

Exclusion criteria will include those listed in the original protocol, including those specific to the use of liraglutide 3.0 mg/d (e.g., family history of medullary thyroid cancer).

Additional exclusion criteria added to the 12-week extension study are specific to the use of phentermine 15 mg/d. They include:

1. Use of monoamine oxidase inhibitors in the past 2 weeks
2. Glaucoma
3. Presence or history of marked agitation
4. History of drug abuse
5. Known hypersensitivity to sympathomimetic amines
6. Current use of selective serotonin re-uptake inhibitors (e.g., fluoxetine, sertraline, etc)
7. Current use of any other weight loss medications (besides liraglutide 3.0 mg/d)
8. History of coronary artery disease

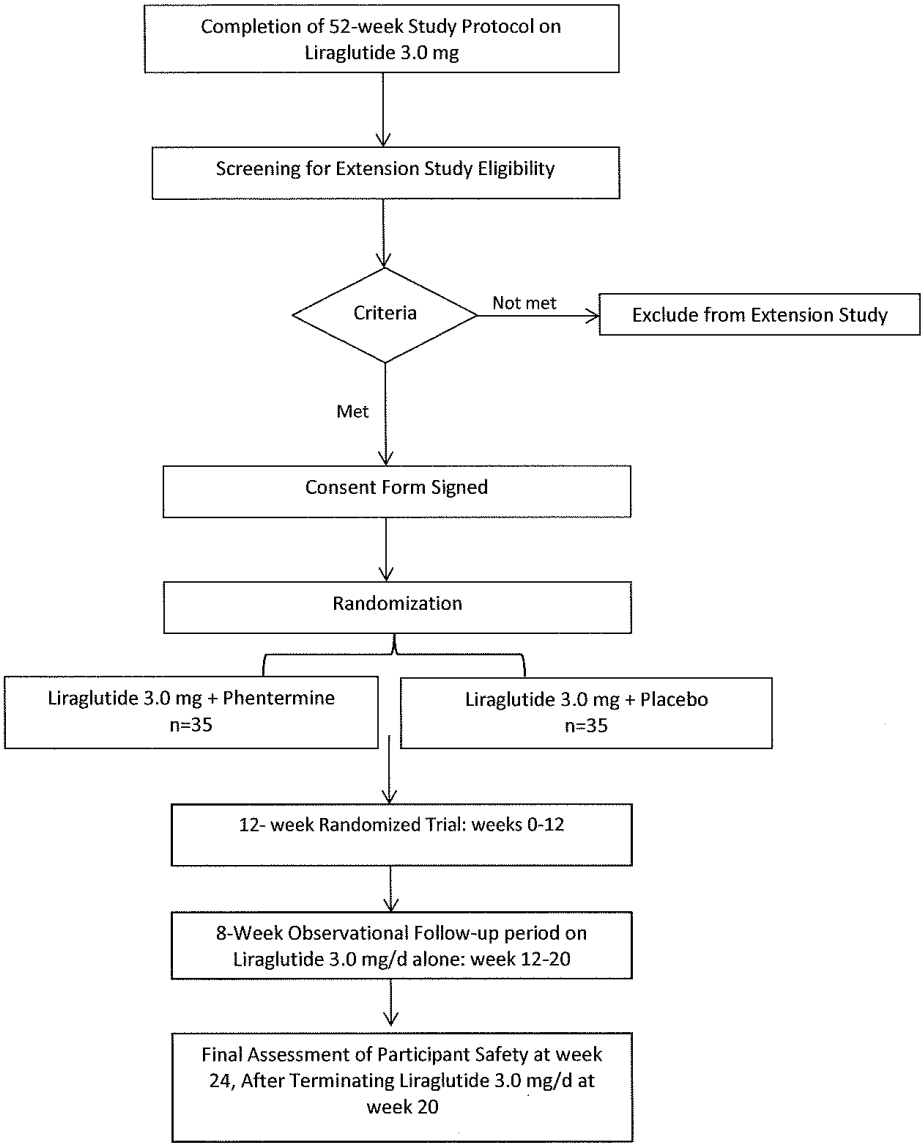
Withdrawal Criteria

Please refer to the original protocol for all information required in this section.

Visit Procedures

Figure 3 shows the flow of subjects through the 12-week extension trial (and the subsequent 8-week observational period on liraglutide 3.0 mg/d). Table 3 presents the schedule of study assessments and treatment visits.

1682 **Figure 3. Extension Study Flow Diagram**



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1685 Table 3. Schedule of Extension Study Assessments and Lifestyle Intervention Counseling Visit

Original 52 Week Study																							Extension Study									
	Weeks																							Weeks								
	Screen	R/1	2	3	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	52		Screen	R/0	2	4	8	12	16	20	24
	Visit Number																							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	25	26	27	28	29	30	31
All subjects																																
Informed consent	X																							X								
Behavioral evaluation	X																															
History and physical	X																							X								
ECG	X																							X								
Blood draw	X														X							X						X				
Labs	X														X							X						X				
Self-reported outcomes		X													X							X			X				X			
Medical Assessment		X			X		X				X				X				X			X			X	X	X	X	X	X	X	X
Lifestyle intervention		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	
Vital signs (Weight, BP, HR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
CMS-Liraglutide Group and Multi-Component Intervention Group Only (CMS + Liraglutide + Meal Replacements)																							***Extension Study Participants***									
Liraglutide provided		X			X		X		X		X		X		X	X	X	X	X	X	X		Liraglutide + phentermine (or placebo) provided		X		X	X				
Multi-Component Intervention Only (CMS + Liraglutide + Meal Replacements)																																
Meal replacements					X	X	X	X	X	X	X	X											Liraglutide only						X	X		

Note. R=randomization. Randomization will be followed immediately by week 1 medical visits and lifestyle intervention sessions. Columns shaded in grey indicate principal outcome assessment visits.

Screening Procedures

All participants in the CMS-Liraglutide and Multi-Component interventions will be informed of the 12-week extension study at the time of their 48-week visit for the original 1-year trial (i.e., 1 month before the trial's conclusion). They will be apprised of the study extension by their lifestyle coach (who include physicians, nurse practitioners, and registered dietitians). The coach will explain the extension study and answer any questions concerning it. Participants interested in participating in the study will meet, immediately following their coaching visit, with the principal investigator or one of his designees who will assess the participants' likely appropriateness for the study and obtain written informed consent from the participant. (Participants in the CMS-Alone group will be informed of the extension, randomized controlled trial and told that it is only open to participants in the two medication groups. They also will be informed of the opportunity to receive 5 additional monthly counseling visits [weeks 4-20] and provide informed consent if they wish to continue to participate.)

Screening Visit

Participants who wish to participate in the extension randomized controlled trial (RCT) will meet at week 52 (of the original trial) with a study physician or nurse practitioner for the final medical visit of the 1-year trial (see Table 1 from the original 1-year protocol). The practitioner will further assess the participants' eligibility for the extension study, and an EKG will be conducted to ensure that the participant has no cardiac abnormalities. Blood pressure and pulse will be checked to ensure that they are within the upper limit of normal (< 160/100 mm Hg, with a resting pulse no greater than 85 beats per minute (BPM), given the possible effects of both liraglutide and phentermine in increasing heart rate). All participants also will have a blood draw at week 52 to examine cardiometabolic risk factors (described in the original protocol), as well as standard blood chemistries (e.g., liver function tests).

Randomization Visit

Participants who appear to meet all eligibility criteria (to be confirmed by the results of blood tests) will be scheduled the following week for a randomization visit for the extension study. They will be instructed to continue to take liraglutide 3.0 mg/d for the week between the screening visit and the randomization visit.

Participants' eligibility status, as well as completion of all questionnaires from the week 52 visit (from the original 1-year trial), will be examined a final time at the beginning of the randomization visit. Participants who remain fully eligible will be randomly assigned to the two medication interventions in equal numbers (i.e., 1:1 ratio). The randomization will be conducted by Dr. Ken Rockwell, director of the Investigational Drug Service at Penn. The randomization will be from stratified blocks, based on whether participants lost $\geq$10 of initial weight during the 1-year trial. This will control for any influence that prior treatment arm had on patients' end-of-treatment weight loss and ensure that the two groups are balanced (on prior weight loss) at the outset of the extension study.

Following randomization, all participants will have a medical visit with the study physician or nurse practitioner who will instruct patients in the two treatment groups in the continued use of liraglutide 3.0 and in the addition of the second medication, which will be presented in capsule form. Participants will be encouraged to take both medications in the morning upon awakening.

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 4 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 Dr. Rockwell, in response to notification from the principal investigator (or study co-investigators) of patients' complaints of symptoms. (With Dr. Rockwell, we successfully used this titration method in a prior randomized placebo-controlled trial of sibutramine for weight loss.[46]) Participants in whom phentermine (or placebo) is terminated will continue to receive liraglutide 3.0 mg/d in an open-label manner, as they have for the prior year.

Following randomization, all participants also will have an individual lifestyle intervention session with their provider to review their diet and physical activity goals

Lifestyle Counseling Visits – All Groups

Participants in both medication groups in the extension study (i.e.,liragltide + phentermine vs liraglutide + placebo) will receive the same program of diet, physical activity, and behavior therapy, as provided during the last 6 months of the original 1-year trial. All participants will be provided 4 brief (15 min), face-to-face visits during the 12 weeks, with visit scheduled at weeks 0 (randomization), 4, 8, and 12. Lifestyle counseling will be delivered by a physician, nurse practitioner (NP) or a registered dietitian (RD) or behavioral psychologist, the latter working incident to an NP or physician. (Participants in the CMS-Alone group will be eligible for this same schedule of lifestyle counseling visits.)

Participants who weigh <250 lb will be prescribed a diet of 1200-1499 kcal/d, comprised of conventional foods, with approximately 15-20% kcal from protein, 20-35% from fat, and the remainder from carbohydrate. (Those who weigh >250 lb will be prescribed 1500-1800 kcal/d.) They will be instructed to continue to record their food and calorie intake daily, using paper-and-pencil diaries or on-line trackers (including MyFitnessPal or Lose-It).

All individuals will be instructed to continue to engage in low-to-moderate intensity physical activity (principally walking or similar aerobic activity) 5 days per week, for at least 180 minutes per week and preferably $\geq$225 minutes/week. Subjects will be instructed to record their activity daily and will receive a traditional pedometer (Yamax, Digi-Walker) if they do not own a smart phone, Fitbit, or other device with which to track their steps.

Missed visits will be rescheduled whenever possible. If the subject is unable to complete the visit in person, a telephone call of 15 minutes may be substituted for the face-to-face meeting. The same meeting format, including a report of the subject's weight, will be followed for phone-delivered sessions as for face-to-face meetings. A growing body of evidence indicates that phone-delivered lifestyle counseling is as effective as face-to-face meetings.

Medical Monitoring Visits

Following randomization, all participants in both medication groups will have brief medical assessments (5-10 minutes) with a physician or nurse practitioner at weeks 2, 4, 8, and 12. At each medical assessment, participant's weight and vital signs will be measured and their response to the medication will be assessed. Study subjects will be asked whether there have been any changes in their health or medications. For all non-study-related medical events, participants will be referred to their own primary care providers. Participants also will be asked about their mood or any thoughts of harming themselves, as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS).[27] In the event of reports of suicidal ideation or disturbances in mood, participants will be referred to the study's psychologist or psychiatrist for further evaluation, as appropriate.

Liraglutide 3.0 mg Continuation Study from Weeks 12 to 20

At the end of week 12 (post-randomization), phentermine and placebo will be terminated, but both groups will remain on liraglutide 3.0 mg/d until week 20. Participants will continue to have both lifestyle counseling and medical visits at weeks 16 and 20 (and those in CMS Alone will be offered counseling visits on the same schedule). We wish to observe, from weeks 12 to 20, the change in body weight that occurs with the termination of phentermine 15 mg/d. At week 20, liraglutide also will be terminated in all participants. At week 24 (post-randomization), all participants will have a final assessment with a physician or nurse practitioner to determine participants' health status.

Assessments for Efficacy

Participants will attend 2 major outcome assessment visits, conducted at randomization (the week 52 visit of the 1-year trial) and week 12.

Primary Efficacy Measure

The primary outcome is % reduction in initial body weight, as measured from randomization to week 12. Secondary outcomes include the proportion of participants who at week 12 lose $\geq$5% or $\geq$10% of randomization weight. Body weight will be measured on a digital scale (to the nearest 0.1 kg) with participants dressed in light clothing, without shoes. Two measurements will be taken on each occasion and averaged. Weight will be measured by an assessor masked to participants' treatment conditions.

Secondary Efficacy Measures

The secondary efficacy measures, to be assessed at week 12 of the extension study, include changes in cardiovascular disease (CVD) risk factors (i.e., blood pressure, triglycerides, LDL and HDL cholesterol, and waist circumference), glycemic control (i.e., fasting blood sugar), mood (PHQ-9), quality of life (i.e., SF-36 and IWQOL-Lite), eating behavior (i.e., Eating Inventory, Eating Disorder Examination-Questionnaire, and Yale Food Addiction Scale), appetite (i.e., visual analogue scales), sleep (i.e., Pittsburgh Sleep Quality Index), and satisfaction with weight loss. All of these measures are described in the original protocol.

A secondary analysis will examine differences between the two randomized groups in changes in weight and other outcomes as measured from participants' original randomization values, when starting the original 1-year trial.

Changes in weight from week 12 to week 20, when participants receive liraglutide alone, will be examined using descriptive statistics.

Assessments for Safety

Safety endpoints include physical examination, adverse events (AEs), standard laboratory tests, and mental health/suicidal behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS). As detailed above, participants in all three groups also will have brief medical visits (5-10 minutes) with a physician or nurse practitioner at weeks 2, 4, 8, 12, 16, and 20 (total of 6 visits). At each medical visit, participant's response to the medication will be assessed. Study subjects will be asked whether there has been any change in their health or medications. They also will be asked about their mood or any thoughts of harming themselves, as determined by the C-SSRS. In the event of adverse mental health events, participants will be referred to the study's psychologist or psychiatrist for further evaluation, if required. For all non-study-related medical events, participants will be referred to their own primary care provider.

Participants will have fasting blood draws (comprehensive metabolic panel, lipids, etc) at screening and week 12 of the extension study. Vital signs (blood pressure and pulse) and weights will be measured at weeks 0 (randomization) and 2, 4, 8, 12, 16, and 20.

Subject Compliance

We will measure subject's medication adherence to liraglutide using injection counts from visual inspection of the dose counter taken from subjects' injection pens. Patients will be instructed to bring the pen to each session, and we will record missed doses and problem solve with patients if they are missing doses. We will track adherence to phentermine/placebo by counting the number of unused capsules at each visit. Patients will be instructed to keep a medication diary, as part of their food and activity monitoring.

STATISTICAL CONSIDERATIONS:

Sample Size Calculation

At week 12 of the extension study, subjects assigned to liraglutide-phentermine are predicted to lose 3.5% (SD=3.5) of randomization weight, while those assigned to liraglutide-placebo are expected to lose 0.0% (SD=0.5). (Both values will be measured as change from randomization to week 12 and do not reflect weight lost in the prior 1-year trial.) These estimates are based on the results previously described by Aronne et al in a study of phentermine plus topirimate and a study of Smith et al in a study of phentermine combined with loracserin.[49,50] Using a sample size equation for longitudinal clustered samples, a randomization sample of 35 subjects in liraglutide-phentermine and 35 subjects in liraglutide-placebo provides >80% power to detect a statistically significant difference ($p < 0.05$, two tailed test) between the two groups. This estimate allows for 10% attrition during the 12-week trial, resulting in approximately 32 treatment completers per group. (The 10% attrition level is conservative; all participants will have demonstrated that they are highly adherent as a result of completing the prior 1-year trial. The ITT longitudinal statistical design will further improve power by allowing the inclusion of available data for non-completers and the adjustment of possible variance reducing baseline covariates. All secondary analyses will be considered exploratory and evaluated at the alpha = 0.05 level. The power analysis was conducted using PASS 11.

Statistical Methods

Preliminary Analyses

All data analyses will proceed using the same principles and methods described in the Statistical Methods section of the original protocol.

Interim Analysis

No interim analyses are planned (in order to maintain full power for the end-of-study comparisons).

Explorative Statistical Analysis for Pharmacogenetics and Biomarkers

No explorative statistical analysis for pharmacogenetics and biomarkers will be performed.

Data Handling and Record Keeping:

The same procedures will be used to address these issues as used in the original trial.

Ethics:

The same procedures will be used to address these issues as used in the original trial.

Study Schedule:

Table 4. Extension Study Timeline

	2017				2018				2019	
First patient screening			9/20							
Last patient randomization						5/28				
Last patient last visit							8/20			
Data collection										
Data analysis/manuscripts									2/28	
Final study reports									2/28	

Study Drugs and Materials:

For the randomized extension trial, participants assigned to liraglutide-phentermine, as well as phentermine-placebo, will need 91 doses (13 weeks x 7 doses per week) of liraglutide. (This includes 1 week of liraglutide to be used between the screening visit [at week 52] and the randomization visit [at week 0]). Subjects will be provided with a 30-day supply of medication (5 pens) at randomization and weeks 4 and 8. Liraglutide will be provided in an open-label manner, as it was throughout the 1-year prior trial.

At the randomization visit (week 0), participants in both medication groups will be provided 15 identical capsules containing either phentermine 8.0 mg/d or placebo (depending upon their treatment assignment). Upon returning at week 2, they will be provided 15 additional capsules containing either phentermine 15.0 mg or placebo. At week 4, and again at week 8, all participants will be provided 30 capsules containing phentermine 15.0 mg or placebo.

Following completion of the 12-week extension trial, all participants will discontinue phentermine (or placebo) but will remain on liraglutide 3.0 mg/d for an additional 8 weeks. Participants will require an additional 56 doses (8 weeks x 7 doses per week) of liraglutide from weeks 12 to 20. Participants will be provided a 30-day supply (5 pens) at both weeks 12 and 16.

Study Medications

The study medications are liraglutide 3.0 mg/d and phentermine 15.0 mg/d (or placebo).

Packaging and Labelling of Study Medications

Liraglutide will be packaged, labelled, and distributed to patients, as it was during the 1-year trial. The medication will be provided by Novo Nordisk as ready-to-use, pre-filled, multi-dose pens by Novo Nordisk in a subject box.
Study drug will be shipped to the Center for Weight and Eating Disorders at the University of Pennsylvania (attention Dr. Tom Wadden) for labeling and packaging. The study drug supplies will be labeled appropriate to their use. The label for the study drug will contain at a minimum:

- Protocol number
- Kit identification number from the randomization scheme
- Instructions for use
- Study drug name

Phentermine (and placebo) will be purchased and then packaged in blinded capsules by Dr. Ken Rockwell, director of the Investigational Drug Service at Penn. Dr. Rockwell has prepared medications before for our Center in this manner. Dr. Rockwell will store all phentermine-placebo at the hospital, to be picked up on a weekly basis by study coordinators and distributed to study patients.

Storage and Drug Accountability of Study Medication

The same procedures will be used to address these issues as used in the original trial.

Randomization and Blinding

Dr. Ken Rockwell from Penn's Investigational Drug Service will generate the randomization code. The first subject to meet the treatment criteria will be assigned the first number in the sequence; each subsequent subject to meet treatment criteria will be assigned the next number in the sequence. This study combines the open-label provision of liraglutide with blinded assignment to phentermine or placebo.

Breaking of Blinded Codes

Dr. Rockwell will be prepared to break the blinded code in the event of patient emergency.

Concomitant Illnesses and Medications:

At trial entry (i.e., the screening visit), we will record details of any concomitant illness (i.e., any illness that is present at the start of the trial) that is present and concomitant medication (i.e., any medication other than the trial product(s) that is taken during the trial, including the screening and run-in periods) in each patient's record. The information collected for each concomitant medication will include the start date, stop date or continuing, and indication. For each concomitant illness, we will record the date of onset, date of resolution or continuing. Any changes in concomitant medication use will be recorded at each visit. If the change influences the subject's eligibility to continue in the trial, the Sponsor will be informed.

Adverse Events:

At each contact with subjects, study personnel will be responsive to reports of adverse events with specific questioning and, as outlined in the procedures section, by physical examination. The investigator will be report all adverse events including serious adverse

events (SAE), suspected unexpected serious adverse reactions (SUSARs), serious adverse drug reactions (SADRs) (as defined below) to the Data Safety and Monitoring Board established for the trial, and to the Penn IRB. 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). Information on study name, patient identification, event (i.e., diagnosis, causality), drug, and reporter identification (e.g., name) will be collected and recorded in the source document (as detailed below). All serious adverse events will be reported to the IRB within 24 hours. The investigator will report to Novo Nordisk all SAEs, SUSARs, and SADRs at the same time such events are reported to regulatory authorities or within 15 days from the investigator becoming aware of such adverse events, whichever comes first.

The PI and his investigative team acknowledge the definition of adverse events (AEs), serious adverse events (SAEs), and other untoward occurrences as spelled out below.

Adverse Event (AE):
An AE is any untoward medical occurrence in a patient or clinical investigation subject administered/using a product and which does not necessarily have to have a causal relationship with this treatment. An Adverse Event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product.

Clinical Laboratory Adverse Event:
A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management, (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

Serious Adverse Event (SAE):
A serious AE is an experience that at any dose results in any of the following:
• Death
• A life-threatening* experience
• In-patient hospitalisation or prolongation of existing hospitalization
• A persistent or significant disability/incapacity
• A congenital anomaly/birth defect
• Suspicion of transmission of infectious agents
• Important medical events that may not result in death, be life-threatening*, or require hospitalisation may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

*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.

Suspected Unexpected Serious Adverse Reaction (SUSAR): A SUSAR is an SAE which is unexpected and regarding as possibly or probably related to the trial/study product by the investigator.

Serious Adverse Drug Reaction (SADR):
An adverse drug reaction (ADR) is an adverse event for which a causal relationship (Possible/Probable relation) between the study drug and the occurrence of the event is suspected. The ADR should be classified as **serious** if it meets one or more of the seriousness criteria.

Medical Events of Special Interest (MESI): A MESI is (1) a medication error (e.g. wrong drug administration or wrong route of administration) or (2) a suspected transmission of an infectious agent via the product

Non-Serious Adverse Event:
A non-serious AE is any AE which does not fulfil the definition of an SAE.

Severity Assessment Definitions:
• Mild: Transient symptoms, no interference with the subject's daily activities
• Moderate: Marked symptoms, moderate interference with the subject's daily activities
• Severe: Considerable interference with the subject's daily activities, unacceptable

Relationship to study medication Assessment Definitions:
• 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

The US PI will be used to evaluate all unexpected events and adverse reactions.

Outcome Categories and Definitions:
• Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
• Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
• Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
• Not recovered
• Fatal
• Unknown

Collection, Recording and Reporting 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 posttreatment follow-up period as stated in the protocol.

Follow-up of Adverse Events
During and following subjects' participation in the study, the investigator and institution will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. (Note: This section of the protocol will be written in consultation with Penn's IRB, Office of Research Services, and Office of Legal Affairs. It will be addressed pending approval of the scientific aspects of the study.)

Pregnancy
Study subjects will be instructed to notify the investigator immediately if they become pregnant. The investigator will report to Novo Nordisk any pregnancy occurring during the trial period. 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.

Precautions/Over-dosage
In case of suspected overdose, subjects will be instructed to call their healthcare provider immediately, as excessive intake of Saxenda may cause severe nausea and vomiting.

Liability and Subject Insurance:
Liability and subject insurance have been addressed in the contract that governed the original 1-year trial. These conditions will continue in the 12-week extension study.

Evaluability of Subjects:
Participants will be excluded from data analysis in the event of pregnancy, amputation, bariatric surgery, or death. Additional criteria associated with subject censorship will be considered prior to initiating recruitment.

Premature Termination of Study:
We believe that it is highly unlikely that the study will be terminated prematurely, given the safety of the intervention and its expected effects. Termination would be considered, however, in view of:

- Unacceptable safety concerns of the study medication
- The benefits observed do not ethically permit the trial to continue

Publication Plan:
We will register the study with a publicly assessable database such as clinicaltrials.gov. An initial report of the findings will be presented at an annual scientific meeting (e.g., American Diabetes Association, The Obesity Society, The American Heart Association). We plan to publish the study results approximately 6 months after study completion.

The report of the primary outcome likely will be submitted to the International Journal of Obesity or the journal Obesity. The study's short duration and small sample size make these journals the most appropriate outlets for publication.

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