

**Short- and Long-term Effects of Once Weekly Semaglutide 2.4 mg on Appetite,
Eating Behavior, and Psychosocial Status:
A 60-week, Double-Blind Randomized Controlled Trial
with an Additional 12-Week Double-Blind End-of-Trial Withdrawal Study**

INVESTIGATOR-SPONSORED STUDY PROPOSAL

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BACKGROUND AND SIGNIFICANCE:

Semaglutide 2.4 mg is a once weekly subcutaneous glucagon-like peptide-1 (GLP-1) receptor agonist currently under investigation for the treatment of overweight and obesity. When administered with monthly lifestyle counseling, semaglutide 2.4 mg produces a mean loss of approximately 15% of baseline weight in 68 weeks (1). These substantial losses are associated with improvements in obesity-related co-morbidities and quality of life (1,2,3).

The proposed mechanisms for the effects of GLP-1 receptor agonists on body weight include reductions in appetite and food reward (4-7). Appetite refers to perceived levels of hunger, fullness, and satiety resulting from both objective (e.g., physiological/homeostatic) and subjective (e.g., learned) experiences. Food reward, on the other hand, is the result of non-homeostatic processes driven by activation of the dopaminergic and opioid systems (4,5). Indicators of the rewarding value of food include the pleasure or hedonic value derived from consuming food and measures of motivation or wanting to eat, including food cravings, and responsiveness to the food environment. Both appetite and reward influence actual energy intake, which decreases after administration of a GLP-1 receptor agonist (4-9).

Consistent with this research, short-term studies of semaglutide have demonstrated reductions in energy intake, appetite, and food reward that may drive its strong initial effects on body weight (8,9). In a recent randomized trial by Friedrichsen and colleagues, subjects assigned to take semaglutide 2.4 mg for 20 weeks consumed 35% fewer calories during an ad libitum lunch meal (ETD: -940 kJ or -225 kcal) than those taking placebo (9). Semaglutide-treated subjects also experienced greater mean increases in fullness and satiety, as well as reductions in hunger and prospective (desired) food consumption. Past-week ratings of appetite and food cravings also improved. These appetitive findings were similar to the effects observed at 12 weeks with the 1.0 mg dose of semaglutide that is currently approved for the treatment of diabetes mellitus (8). This latter study also found that semaglutide produced short-term reductions in food reward, including implicit wanting, explicit liking, and cravings, particularly for non-sweet, high-fat foods.

These short-term studies could not assess whether semaglutide has long-term effects on energy intake, appetite, or food reward that support the maintenance of its large initial weight losses. In a 52-week study of the appetitive effects of another GLP-1 receptor agonist, liraglutide 3.0 mg, Tronieri and colleagues demonstrated that the large initial reductions in hunger and food preoccupation (as well as increases in fullness) experienced by liraglutide-treated subjects early in treatment were not maintained at week 40 or week 52, despite the maintenance of relatively greater weight losses in the liraglutide-treated subjects, compared with lifestyle modification alone, at those times (10). In that study, mean weight loss in the liraglutide-treated group reached its nadir at week 40 and remained relatively stable through week 52. The Tronieri et al. study did not include a direct measure of energy intake, so it is unclear whether changes in objective measures of appetite also would have been attenuated later in treatment.

The long-term appetitive effects of anti-obesity medications like semaglutide are important to assess because these drugs are intended to be taken chronically to maintain lost weight, not just to produce an initial weight reduction (11,12). However, patients' willingness to continue to take an anti-obesity medication is likely to wane if they believe that it is no longer working based on perceptions of diminished appetite control. Indeed, patients' beliefs about medication effectiveness have been identified as a predictor of discontinuation (13). The poorest long-term treatment adherence has been observed with treatments designed to prevent recurrence of a condition (13), which is the objective of long-term obesity management. Assessing whether the subjective appetitive benefit of semaglutide is diminished once weight loss slows after approximately 52 weeks of treatment will allow health care providers to better anticipate their patients' experiences when taking the medication. This information will allow providers to inform their patients whether the medication's effects on energy intake and food reward persist beyond the point at which subjective appetite benefits decline. This possibility is suggested by the maintenance of lost weight at week 52 in the Tronieri et al study (10) and at 68 weeks with semaglutide 2.4 mg (1), as well as by longer-term studies showing continued weight maintenance at 3 years with liraglutide (10, 14). In this case, patients could be informed that, after the first year of taking medication, they should expect to experience hunger/fullness signals that feel similar to their pre-treatment levels, but they will continue to eat less food than they did before treatment.

In addition to lengthening the period of appetite assessment, the present study will include measures of food reward, which have not yet been evaluated in either the short- or long-term at the 2.4 mg dose. Reward-related outcomes will include both explicit measures of responsiveness to the food environment and implicit measures of food wanting. A supportive secondary aim will evaluate whether the initial reductions in food cravings seen at 20 weeks with semaglutide 2.4 mg in the Friedrichsen et al. study (9) are maintained with long-term treatment. *We expect that this set of findings will provide conclusive evidence that semaglutide makes people less vulnerable to the toxic food environment by reducing appetite, food reward, cravings, and, ultimately, energy intake in both the short- and long-term.*

The present study also will evaluate associated measures of eating behavior such as dietary self-efficacy, cognitive restraint, and dietary disinhibition, as well as mood and disordered eating symptoms, including loss-of-control eating, binge eating, and drive for thinness. Large weight losses, as produced by very-low-calorie diets (VLCDs) or bariatric surgery, may be associated with adverse changes in these latter eating behaviors (15-18), and they accordingly should be assessed in patients treated by semaglutide 2.4 mg. Evaluating these outcomes will provide important evidence for health care providers who are concerned about possible adverse behavioral or psychosocial consequences of marked weight loss with semaglutide 2.4 mg. In one of our prior studies of a behavioral intervention, patients who lost a mean of 12% of their initial weight with a portion-controlled low-calorie diet *reported significant improvements in eating behavior, body image, and mood* and did not, on average, have more frequent binge eating episodes than non-dieting subjects (19). One subject (from an N of 41), however, who lost 27% of her initial weight, reported significant symptoms of depression and multiple episodes of

binge eating after 40 weeks of treatment. This finding suggests the need to assess the possibility of such rare events in patients who achieve substantial weight losses with semaglutide 2.4 mg. *However, we expect that average mood and symptoms of disordered eating, such as loss of control, will improve with semaglutide*, consistent with the mean improvements seen with other weight loss interventions (19-23).

Study 1: Long-term Treatment Trial (Weeks 0-60)

The proposed long-term treatment trial will randomly assign (in a 3:2 semaglutide:placebo ratio) 120 subjects with a body mass index (BMI) ≥ 30 kg/m², or ≥ 27 kg/m² with ≥ 1 obesity-related co-morbidities, to 60 weeks of: 1) placebo with moderate intensity lifestyle intervention (as used in STEP 1); or 2) semaglutide 2.4 mg with the same lifestyle intervention. (Assignment to these conditions in a 3:2 ratio will allow us to have a sufficient number of semaglutide-treated subjects for re-randomization in the subsequent double-blinded re-randomized medication withdrawal trial described below.) All subjects will receive 60 weeks of trial product, which will be up-titrated over 16 weeks in those assigned to semaglutide 2.4 mg. They will complete assessments of energy intake, appetite, food reward, mood, symptoms of disordered eating, and anthropomorphic measurements at baseline (week 0) and weeks 20, 40, and 60. The purpose of the week 20 assessment is to establish whether subjects initially achieve improvements in energy intake and appetite of a similar magnitude to those observed in previous studies (8, 9) and to evaluate semaglutide's effect on food reward at the 2.4 mg dose, which was not tested previously.

Our primary aim in the initial long-term treatment trial will be to compare the long-term effect of semaglutide 2.4 mg vs placebo on ad libitum energy intake (in kcal) during a buffet lunch meal at weeks 20, 40, and 60. Confirmatory secondary aims will test the effect of semaglutide 2.4 mg at weeks 20, 40 and 60 on subjective appetite ratings (both measured during a standardized breakfast in the lab and as experienced more globally over the past week), explicit food reward, as measured with the Power of Food Scale (24), and implicit food reward, as measured with the Leeds Food Preference Task (25, 26). Measures of food cravings, mood, eating disorder symptoms, and self-report measures of eating behavior will be considered supportive secondary endpoints and will provide additional evidence of the medication's safety and efficacy.

Study 2: Re-randomized Medication Withdrawal Trial (Weeks 60-72)

Ideally, semaglutide 2.4 mg and other anti-obesity medications should be used indefinitely to maintain weight loss and improvements in health. However, in clinical practice, anti-obesity medications are often terminated by the patient or physician after an initial weight loss is achieved (27). The STEP 4 withdrawal trial demonstrated that subjects gained weight after being randomly assigned to discontinue semaglutide (28). Cardiometabolic risk factors and quality of life also worsened between week 20 (randomization) and week 68 in the STEP 4 participants who were switched from semaglutide to placebo. It also has been hypothesized that large weight losses like those achieved with semaglutide may adversely affect subsequent energy balance regulation. A

study by Sumithran et al. (29) found that patients who lost 13.5 kg with a 10-week VLCD reported increases in appetite above baseline levels at both post-treatment and 1-year follow-up. In light of these findings, physicians and patients may be concerned that discontinuing semaglutide could have adverse effects on physical or mental health and appetite, either due to the withdrawal of the medication or to the large weight losses achieved.

The deterioration in cardiometabolic risk and quality of life observed in STEP 4 subjects who were switched from semaglutide to placebo was generally modest; subjects did not appear to return to their baseline levels, as measured at the beginning of the 20-week semaglutide run-in period (28). In other words, STEP 4 subjects who were switched from semaglutide to placebo at week 20, and regained weight, seemed to have been no worse off (and likely were better off) at week 68 than they were at baseline. However, due to the absence of an untreated control group, STEP 4 could not truly evaluate whether subjects who were withdrawn from semaglutide would have differed at week 68 from individuals who had never received the medication at all. A randomized comparison would provide a more rigorous demonstration that having started and stopped the medication had done no harm, in terms of changes in quality of life and other outcomes.

We seek to capitalize on the long-term, placebo-controlled design of Study 1 by conducting a separate, follow-up, 12-week, re-randomized medication withdrawal trial (Study 2) to compare subjects who discontinue semaglutide 2.4 mg to those who have never received active medication. If semaglutide is shown to produce long-term reductions in appetite, food reward, and eating behavior, those benefits would be expected to wane after the medication is withdrawn. *Despite this potential rebound in appetite and body weight, we do not expect that semaglutide-treated subjects who discontinue the medication will report greater absolute levels of appetite or of dysfunctional eating behavior or mood at the end of the 12-week re-randomization trial than will subjects who had never received semaglutide 2.4 mg during either the original 60-week study or the 12-week continuation study (i.e., continuous-placebo patients). In short, we do not believe that treatment with semaglutide 2.4 mg, its associated weight loss, or any potential weight regain with medication discontinuation will have harmed participants long-term.* Supportive data from the Look AHEAD study, for example, found that HbA1c levels in participants who had lost and regained approximately 12% of body weight were still significantly lower at 4-year follow-up than those of participants in the usual care group who had not lost weight (30). This led the authors to conclude that “it is better to have lost and regained than to have never lost at all.”

Therefore, the 12 week, double-blinded, re-randomized medication withdrawal trial (Study 2; cumulative weeks 60 - 72) will compare week-72 measures of energy intake, appetite, food reward, mood, and symptoms of disordered eating in subjects originally assigned to semaglutide 2.4 mg who are switched to placebo at week 60 (i.e., semaglutide-to-placebo group) with week-72 measures in subjects originally randomized to placebo at week 0 (who remain on it through the re-randomized treatment period, i.e., continuous-placebo group). Our focus on the continuous-placebo group for our primary comparison is designed to address health care providers’ potential concerns about the

possibility of adverse post-treatment effects of discontinuing semaglutide. The discovery of adverse appetitive or behavioral events (*which is contrary to our hypotheses*) could argue for down-titration of semaglutide when stopping the medication, just as it is up-titrated to minimize adverse gastrointestinal events.

After completion of Study 1 at week 60, subjects who were originally assigned to semaglutide 2.4 mg will be re-randomized (in a 1:4 semaglutide:placebo ratio) to receive either continued semaglutide or placebo for an additional 12 weeks (Study 2). All subjects who were originally assigned to placebo will continue with that treatment from week 60 to week 72. The goal of this re-randomized medication withdrawal period will be to compare the 80% of subjects originally assigned to semaglutide 2.4 mg who receive placebo at week 60 (semaglutide-to-placebo group) to the subjects originally randomized to placebo (continuous-placebo group) on all primary and secondary outcome measures at week 72 (after controlling for Study 1 baseline/week 0 values). We hypothesize that the semaglutide-to-placebo group will not have greater energy intake, appetite, food reward, or worse eating behavior and psychosocial outcomes than the continuous-placebo subjects at the end of the 12-week re-randomized trial. We anticipate that 82% of Study 1 subjects (59 out of 72 subjects originally assigned to semaglutide 2.4 mg and 39 of 48 subjects originally assigned to placebo) will complete Study 1 on drug and enroll in Study 2. All subjects will terminate trial product at week 72 and return to clinic for a final safety visit at week 76. In the case that a subject is not able to return to the office for the week 76 safety visit, the study team will reach out by phone to verbally assess changes in the subject's health since week 72, including administration of the C-SSRS.

Of note, Study 2 comparisons will focus on differences between the groups at week 72 itself, and not on comparing changes between week 60 and week 72. Instead of demonstrating that the removal of the medication results in the deterioration of the benefits that it produces (as was done in STEP 4), our goal is to demonstrate that at the withdrawal period endpoint, week 72, participants who discontinue semaglutide are no worse off (as measured by absolute values of appetite, eating behavior, and mood) than individuals who were never exposed to the medication. Consistent with this aim, participants who are randomized to continue taking semaglutide from week 60 to week 72 (i.e., semaglutide-to-semaglutide group) will not be the focus of any statistical comparisons. (We note that ideally all semaglutide-treated subjects would receive placebo during the 12-week, post-trial, re-randomized treatment period in order to provide the largest sample of subjects to test for potential adverse behavioral effects during this period. However, in order to have a truly double-blind re-randomization at week 60 [for both investigators and subjects], a small number of subjects must be assigned to continued semaglutide treatment.)

SPECIFIC OBJECTIVES:

Primary Objective:

Study 1: Long-term treatment trial (weeks 0-60)

Objective 1: To compare changes, relative to baseline, in energy intake at weeks 20, 40, and 60 in subjects randomly assigned to semaglutide 2.4 mg vs placebo.

Secondary Objectives:

Study 1: Long-term treatment trial (weeks 0-60)

Objective 2: To compare changes, relative to baseline, in subjective appetite (as assessed in the laboratory and globally over the past week) at weeks 20, 40, and 60 in subjects randomly assigned to semaglutide 2.4 mg vs placebo.

Objective 3: To compare changes, relative to baseline, in explicit and implicit measures of food reward at weeks 20, 40, and 60 in subjects randomly assigned to semaglutide 2.4 mg vs placebo.

Objective 4: To compare changes, relative to baseline, in eating behavior, food cravings, mood, eating disorder symptoms, and body weight at weeks 20, 40, and 60 in subjects randomly assigned to semaglutide 2.4 mg vs placebo.

Study 2: Re-randomized medication withdrawal trial (weeks 60-72)

Objective 1: To compare energy intake at week 72, controlling for baseline (week 0) intake, in the semaglutide-to-placebo group (i.e., switched from semaglutide to placebo at week 60) vs the continuous-placebo group (i.e., taking placebo since baseline).

Objective 2: To compare subjective appetite (as assessed in the laboratory and globally over the past week) at week 72, controlling for baseline (week 0) appetite, in the semaglutide-to-placebo group vs the continuous-placebo group.

Objective 3: To compare explicit and implicit measures of food reward at week 72, controlling for baseline (week 0) food reward, in the semaglutide-to-placebo group vs the continuous-placebo group.

Objective 4: To compare eating behavior, food cravings, mood, eating disorder symptoms, and body weight at week 72, controlling for baseline (week 0) values, in the semaglutide-to-placebo group vs the continuous-placebo group.

RESEARCH DESIGN AND METHODS

Study Hypothesis (hypotheses):

Study 1: Long-term treatment trial (weeks 0-60)

The long-term treatment trial has the following **primary aim and hypothesis:**

Primary Aim 1. To compare changes, relative to baseline, in energy intake at weeks 20, 40, and 60 in subjects randomly assigned to once weekly subcutaneous semaglutide 2.4 mg vs placebo.

Long-term-H₁: We hypothesize that subjects randomized to semaglutide 2.4 mg (n = 72) will have significantly greater reductions from baseline in ad libitum energy intake (kcal) at weeks 20, 40, and 60 than those assigned to placebo (n = 48).

The long-term treatment trial has the following **confirmatory secondary aims and hypotheses**.

Aim 2. Secondary aim 2 is to compare changes, relative to baseline, in subjective appetite at weeks 20, 40, and 60 in subjects randomly assigned to semaglutide 2.4 mg vs placebo.

Long-term-H₂: We hypothesize that subjects randomized to semaglutide 2.4 mg (n = 72) will have a significantly greater improvement from baseline in both laboratory-based and global subjective appetite at weeks 20, 40, and 60 than those assigned to placebo (n = 48).

Aim 3. Secondary aim 3 is to compare changes, relative to baseline, in explicit and implicit measures of food reward at weeks 20, 40, and 60 in subjects randomly assigned to semaglutide 2.4 mg vs placebo.

Long-term-H₃: We hypothesize that subjects randomized to semaglutide 2.4 mg (n = 72) will have a significantly greater reductions from baseline in both explicit and implicit measures of food reward at weeks 20, 40, and 60 than those assigned to placebo (n = 48).

The long-term treatment trial has the following **supportive secondary aims and hypotheses**.

Aim 4. Secondary aim 4 is to compare changes, relative to baseline, in eating behavior, food cravings, mood, eating disorder symptoms, and body weight at weeks 20, 40, and 60 in subjects randomly assigned to semaglutide 2.4 mg vs placebo.

Long-term-H₄: We hypothesize that subjects randomized to semaglutide 2.4 mg (n = 72) will have significantly greater improvements from randomization in food cravings, eating behavior (dietary self-efficacy, cognitive restraint, and dietary disinhibition), mood, eating disorder symptoms (binge eating, loss-of-control eating, and drive for thinness), and body weight (kg) at weeks 20, 40, and 60 than those assigned to placebo (n = 48).

Study 2: Re-randomized medication withdrawal trial (weeks 60-72)

The re-randomized medication withdrawal trial has the following **supportive secondary aims and hypotheses**. Sample sizes for the comparisons below were estimated assuming 18% attrition during the treatment trial. Approximately 59 of the 72 subjects assigned to take semaglutide 2.4 mg in Study 1 are expected to enroll in Study 2. In Study 2, approximately 12 out of those 59 subjects will be treated with semaglutide and 47 with

436 placebo after re-randomization at week 60. An estimated 39 of the 48 subjects originally
437 assigned to placebo in Study 1 will continue with that treatment in Study 2.
438

439 **Aim 1.** The primary aim is to compare energy intake at week 72, controlling for
440 baseline intake, in the semaglutide-to-placebo group vs the continuous-placebo group.

441 **Re-randomized-H₁:** We hypothesize that the semaglutide-to-placebo group (n = 47)
442 and the continuous-placebo group (n = 39) will not differ significantly in ad libitum
443 energy intake (kcal) at week 72, controlling for baseline (week 0) intake. (Differences
444 between these two groups and those who remain on semaglutide 2.4 mg at week 72
445 will not be subjected to statistical analysis because of the small number of subjects
446 who remain on semaglutide 2.4 mg, n = 12).
447

448 **Aim 2.** Secondary aim 2 is to compare subjective appetite at week 72, controlling for
449 baseline appetite, in the semaglutide-to-placebo group vs the continuous-placebo
450 group.

451 **Re-randomized-H₂:** We hypothesize that the semaglutide-to-placebo group (n = 47)
452 and the continuous-placebo group (n = 39) will not differ significantly in either
453 laboratory-based or global subjective appetite at week 72, controlling for baseline
454 (week 0) appetite.
455

456 **Aim 3.** Secondary aim 3 is to compare explicit and implicit measures of food reward
457 at week 72, controlling for baseline food reward, in the semaglutide-to-placebo group
458 vs the continuous-placebo group.

459 **Re-randomized-H₃:** We hypothesize that the semaglutide-to-placebo group (n = 47)
460 and the continuous-placebo group (n = 39) will not differ significantly in either
461 explicit or implicit measures of food reward at week 72, controlling for baseline
462 (week 0) food reward.
463

464 **Aim 4.** Secondary aim 4 is to compare food cravings, eating behavior, mood, eating
465 disorder symptoms, and body weight at week 72, controlling for baseline values, in
466 the semaglutide-to-placebo group vs the continuous-placebo group.

467 **Re-randomized-H₄:** We hypothesize that the semaglutide-to-placebo group (n = 47)
468 and the continuous-placebo group (n = 39) will not differ significantly in food
469 cravings, eating behavior, mood, and eating disorder symptoms at week 72,
470 controlling for baseline (week 0) measures. We hypothesize that the semaglutide-to-
471 placebo group will have lower body weight than the continuous-placebo group at
472 week 68, controlling for baseline body weight.
473

474 **Endpoints:**

475 *Study 1: Primary endpoint*

476

- 477 • Change from baseline to weeks 20, 40, and 60 in ad libitum energy intake (in
478 kcal) during a buffet lunch meal (consumed 4 hours after a standardized breakfast
479 meal) (8,9).
480

481 ***Study 1: Confirmatory secondary endpoints***

482
483 Aim 2 (subjective appetite) endpoints will be change from baseline to weeks 20, 40, and
484 60 in:

- 485 • Laboratory-based subjective appetite (i.e., appetite when fasting and in response
486 to food consumption [area under the curve]) will be measured as a composite
487 score of visual analogue scale (VAS) ratings of hunger, fullness, satiety, and
488 prospective food consumption (31,32) recorded when fasting and at 30-minute
489 intervals for 4 hours after consuming a standardized breakfast meal.
- 490
491 • Global perceptions of everyday appetite (e.g., hunger, fullness, food
492 preoccupation) over the past week, as measured using the Control of Eating
493 Questionnaire (COEQ) (8,33). (Exploratory comparisons will evaluate differences
494 between the groups in global subjective appetite at all other assessments from
495 week 4 to week 60 of the long-term treatment period.)

496
497 Aim 3 (food reward) endpoints will be change from baseline to weeks 20, 40, and 60 in:

- 498 • Explicit responsiveness to the food environment measured by the summary score
499 of the Power of Food Scale (15-item version) (24).
- 500
501 • Implicit food wanting of high-fat, savory foods measured using the Leeds Food
502 Preference Task (25,26). (Previous research found the strongest effects for
503 implicit preference of high-fat savory foods. Supportive secondary comparisons
504 will evaluate differences between the groups in implicit preference for the other
505 three food categories: high-fat sweet, low-fat savory, and low-fat sweet.)

506
507
508 ***Study 1: Supportive secondary endpoints***

509
510 Aim 4 will assess change from baseline to weeks 20, 40, and 60 in:

- 511
512 • Food cravings over the past week measured using the Control of Eating
513 Questionnaire (COEQ) (8,33). Three factors will be computed from the COEQ:
514 craving control, craving for sweet foods, craving for savory foods. (Exploratory
515 comparisons will evaluate differences between the groups in individual COEQ
516 items at these time points, and in factor scores at all other assessments from week
517 4 to week 60 of the long-term treatment period.)
- 518
519 • Food cravings as measured by the General Food Cravings Questionnaire – Trait
520 (34). A total score and four subscales will be computed: preoccupation with food,
521 loss of control, positive outcome expectancy, and emotional craving.
- 522
523 • Explicit food liking measured during the Leeds Food Preference Task (25,26)
- 524
525 • Eating behaviors including cognitive restraint and dietary disinhibition (Eating
526 Inventory) (35) and weight-related self-efficacy (WEL-short form) (36)

- Mood as assessed using the PHQ-9 (37)
- Symptoms of disordered eating, including clinician-rated binge eating frequency (sum of objective and subjective binge eating frequency; EDE) (38), self-reported loss-of-control eating (Loss of Control Eating Scale [LOCES]) (39), and drive for thinness (Eating Disorder Inventory [EDI]) (40).
- Body weight (kg)

Study 2: Supportive secondary endpoints

Supportive secondary endpoints for the re-randomized treatment period are week-72 measures of all of the above primary, confirmatory secondary, and supportive secondary endpoints.

Study 1 and Study 2: Exploratory endpoints

Change from baseline to weeks 20, 40, and 60, and measures at week 72 of:

- Ratings of food palatability and of nausea, thirst, and wellbeing fasting and in the 4 hours after consuming the standard breakfast meal (31,33).
- Food addiction symptoms (Yale Food Addiction Scale) (41)
- Body image satisfaction (Body Satisfaction Scale) (42)
- Weight-related self-stigmatization (Weight Bias Internalization Scale) (43)

An additional exploratory comparison will examine changes in appetite and food cravings as measured by the Control of Eating Questionnaire every 4 weeks throughout both treatment periods.

Study Type:

Study 1 is a 60-week, single center, double-blinded, randomized controlled, parallel group design trial (i.e., long-term treatment period), and Study 2 is a separate, follow-up, 12-week, double-blind, medication withdrawal trial (i.e., re-randomized treatment period). In Study 1, subjects will receive semaglutide 2.4 mg or placebo for 60 weeks to assess changes in energy intake, subjective appetite, food reward, eating behavior, mood, and eating disorder symptoms. Following the completion of Study 1 at week 60, all participants who remain on drug will be enrolled in Study 2. Semaglutide-treated subjects will be re-randomized to receive placebo or semaglutide 2.4 mg for an additional 12 weeks to evaluate the effects of medication termination on these outcomes. All subjects originally assigned to placebo will continue with that medication during the

12-week double-blinded re-randomized treatment trial. All subjects will terminate trial product at cumulative week 72 and will return to clinic for a final safety visit at week 76.

Subjects will be a total of 120 men and women, aged 18-70 years, with a BMI of 30 kg/m² or above (or ≥ 27 kg/m² with an obesity-related comorbidity). Subjects will attend a screening visit in which they complete a behavioral evaluation and a medical screening. Eligible subjects will then complete a baseline assessment of energy intake, appetite, and food reward and be randomly assigned in a 3:2 semaglutide:placebo ratio to: 1) placebo with moderate intensity lifestyle intervention (as used in STEP 1); or 2) semaglutide 2.4 mg with the same lifestyle intervention. All subjects will receive 60 weeks of trial product in Study 1, which will be up-titrated over the first 16 weeks. They will be provided 15-minute lifestyle counseling sessions every 2 weeks from week 0 (baseline/randomization) to week 4 and every 4 weeks from week 5 to week 60 (17 total visits).

Following the end of Study 1, subjects who complete a week 60 assessment and are taking the trial product at that time will be followed for an additional 12-week, re-randomized treatment trial. We anticipate that 82% of Study 1 subjects (59 of the 72 semaglutide-treated subjects and 39 of the 48 placebo-treated subjects) will be eligible for Study 2. This 12-week period will evaluate, in a double-blinded fashion, endpoint (week 72) differences in energy intake, appetite, food reward, eating behavior, mood, and eating disorder symptoms between subjects who stop taking semaglutide and those who have received continuous placebo. Subjects who were originally assigned to semaglutide 2.4 mg in Study 1 will be re-randomized at week 60 (in a 1:4 semaglutide: placebo ratio) to receive either continued semaglutide or placebo 2.4 mg during the 12-week treatment period in Study 2. All of the subjects who were originally assigned to placebo in Study 1 will continue with that treatment from week 60 to week 72 of Study 2. Figure 1 illustrates subject flow through the study. Subjects enrolled in the re-randomization period will return to clinic for a final safety visit at week 76.

Outcome assessments including ad libitum energy intake, subjective measures of appetite, food reward, eating behavior, mood, and eating disorder symptoms will occur at weeks 0, 20, 40, and 60 of Study 1 and at week 12 (72 weeks from original randomization) of the re-randomized treatment period. Measurements of body weight, waist circumference, blood pressure, pulse, and global, past-week appetite and food cravings (COEQ) also will be collected every 4 weeks throughout both treatment studies.

Rationale for Study Design

The goals of Study 1 are to assess the long-term effects of semaglutide 2.4 mg on energy intake, appetite, and food reward, as well as to investigate the medication's effects on eating behaviour and psychosocial outcomes. Our previous 1-year study of liraglutide found that the initial improvements in subjective appetite seen following the dose titration period were not maintained after week 40, when weight loss in the liraglutide-treated group reached its nadir (10). The 60-week duration of the present study is designed to allow us to evaluate whether the appetitive benefits of semaglutide 2.4 mg persist after the point at which mean weight loss begins to plateau. Because our treatment protocol

was designed to match that used in STEP 1, we estimated that the weight loss nadir would occur at approximately week 60, rather than at week 40 (as seen with liraglutide) (1, 25). We scheduled our final assessment at week 60 in order to ensure that we will assess the primary and secondary outcomes at or beyond the weight loss nadir. We believe that a shorter study would not allow us to adequately capture the long-term appetitive effects of semaglutide 2.4 mg, particularly at the point at which perceived appetite and objective energy intake might diverge.

The short-term appetitive benefits of semaglutide 2.4 mg have recently been described by Friedrichsen et al. (9), including 20-week measures of energy intake, laboratory-based and global subjective appetite, and past-week food cravings. *The present treatment trial distinguishes itself by focusing on the medication's long-term effects, by evaluating the effects of semaglutide on food reward at the 2.4 mg dose (which was not tested previously), and by including additional eating behavior and psychosocial outcomes which are likely to be of interest to health care providers (and scientists).* Because previous evidence suggests that the subjective appetitive effects of GLP-1 receptor agonists may decline in long-term treatment (10), these findings will have important clinical implications for the long-term use of semaglutide 2.4 mg. As noted in our aims section, we plan to compare the treatment groups at week 20 in the present study, even though these comparisons will replicate previous results. Establishing the effect size of the energy intake and appetite outcomes at week 20 in our sample will provide important context for interpreting the week 40 and week 60 results. Without this information, we would not be able to determine whether smaller effect sizes at week 40 and week 60, if observed, are attributable to the medication's effects waning over time or to a weaker initial benefit at week 20 in our sample.

The 12-week, double-blind re-randomized treatment trial (Study 2) enhances the novelty of the present proposal by allowing us to evaluate whether participants who are withdrawn from semaglutide 2.4 mg (semaglutide-to-placebo group) differ on energy intake, appetite, food reward, eating behavior, and psychosocial outcomes from those who never took the medication (continuous-placebo group). Consistent with the findings of STEP 4 (28), we expect that the semaglutide-to-placebo group will not maintain the full appetitive benefits of semaglutide after the medication is stopped at week 60. We therefore anticipate that any improvements achieved with semaglutide in Study 1 will begin to decline between week 60 and week 72 in semaglutide-treated participants who are switched to placebo. However, we do not believe that the semaglutide-to-placebo group will have worse appetite, food reward, eating behavior, or psychosocial status at week 72 than will the participants who were maintained on placebo for the full 72 weeks. In other words, we expect that the medication's benefits will not be fully maintained at week 72 but do not expect that the medication's withdrawal will produce disturbances in mood, eating, or psychosocial outcomes in excess of the levels observed in placebo-to-placebo participants. Instead of comparing changes from week 60 to week 72 in the semaglutide-to-semaglutide and semaglutide-to-placebo groups, which would largely replicate the findings of STEP 4, we seek to establish that the medication has in fact done no harm by comparing the week-72 endpoint in semaglutide-to-placebo and continuous placebo patients. We hope that these findings will address health care providers' and

patients' potential concerns about the possibility of adverse post-treatment effects of semaglutide (or of the large weight losses achieved with that medication) by showing that any relative rebounds in appetite leave participants with no greater hunger or disordered eating than they would otherwise have had.

The duration of the re-randomized treatment period (Study 2) was selected based on the 1-week half-life of semaglutide. Subjects will take their final dose of the medication that they were originally assigned in the treatment trial during the week prior to their week 60 assessment. Because the trial product is taken once weekly, semaglutide-to-placebo subjects will not start taking placebo until their week 61 dose. Approximately 6 half-lives are required for complete drug elimination; thus, residual effects of the medication could last through week 66. Of note, the Eating Disorder Examination assesses binge eating episodes and other disordered eating over the previous 28-day period. We selected week 72 as the re-randomized treatment period endpoint so that the final assessment will occur at least 4 weeks after semaglutide-to-placebo participants are considered to be fully off drug.

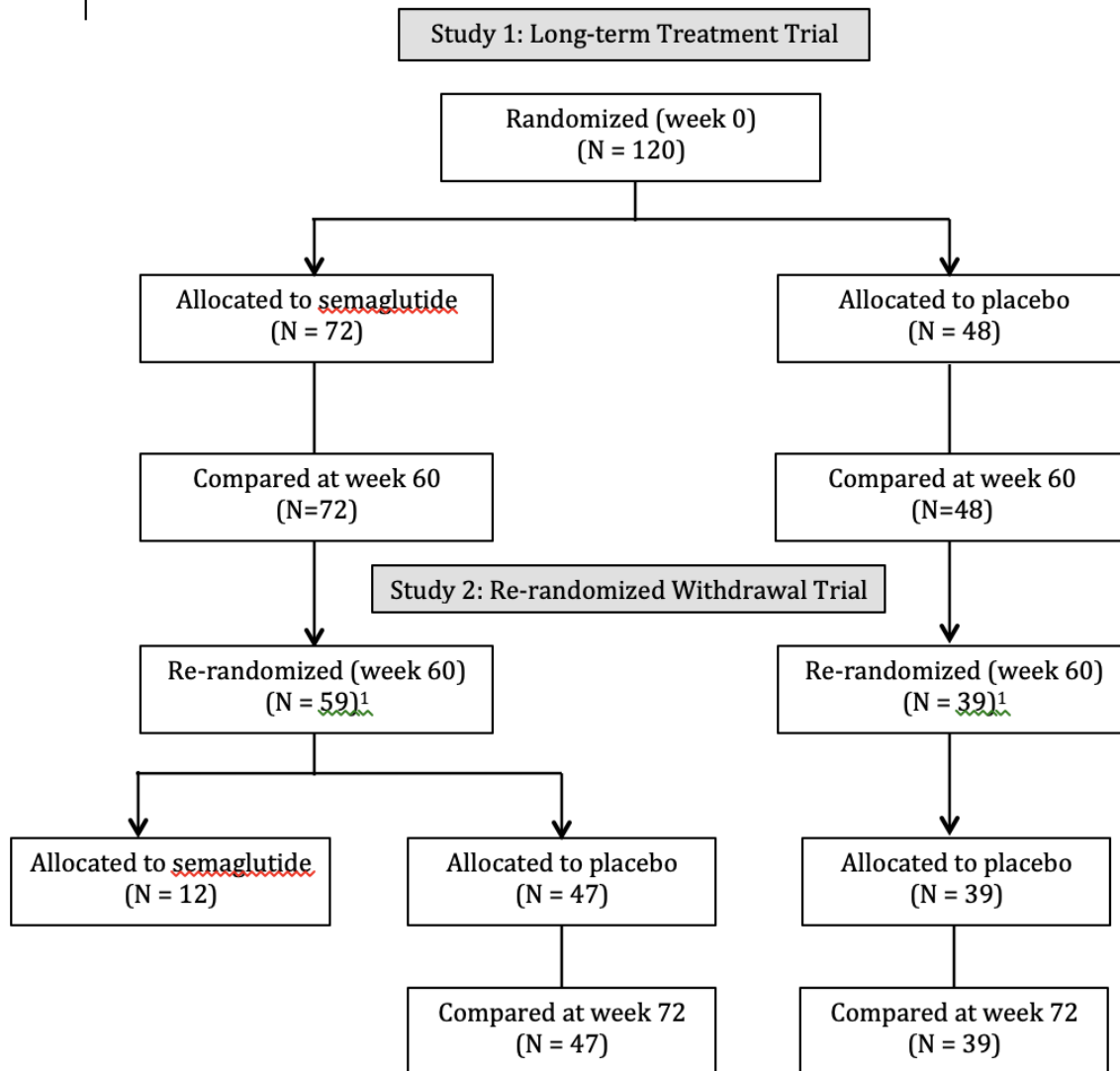
From a participant perspective, Study 1 and Study 2 will be described as two phases of the same trial. During the initial consenting process in Study 1, subjects will be informed that they will take a trial product for a total of 72 weeks. They also will be informed during consenting that semaglutide-treated subjects will be re-randomization 1:4 to semaglutide or placebo at week 60.

Because we do not expect to find differences between the semaglutide-to-placebo and continuous-placebo groups at week 72, we ideally would propose to test non-inferiority for these effects. However, we currently lack pilot data with which to power such outcomes. Additionally, the sample sizes required for a non-inferiority design would be prohibitive and costly, particularly for a trial that requires intensive assessments. We therefore will not be able to demonstrate conclusively that there are no differences between the semaglutide-to-placebo and continuous-placebo groups. However, we believe that these data will be able to provide a clinical impression of whether appetite, eating behavior, and mood are adversely affected by the termination of semaglutide 2.4 mg. (We reiterate that we think the medication should be used indefinitely to facilitate the maintenance of weight loss and improvements in health. However, clinical experience suggests that many patients will discontinue the medication when their weight loss plateaus (27). Practitioners and their patients, as well as scientists, would benefit from knowing the potential changes in appetite, eating behavior, and mood, as well as weight, that may occur in terminating the medication.)

In order to ensure that there will be an adequate number of semaglutide-to-placebo subjects for comparison at week 72 of Study 2, we initially will allocate subjects in Study 1 (the 60-week treatment trial) to semaglutide vs placebo at a 3:2 ratio (ensuring that the size of the semaglutide-treated group is large enough for re-randomization). We then will re-assign the semaglutide subjects to either continued semaglutide or placebo at a 1:4 ratio at week 60. By using these allocation ratios, we anticipate that the size of the semaglutide-to-placebo group will be slightly larger than the continuous-placebo group at

week 72 (Figure 1). By re-allocating a small number of subjects to semaglutide-to-semaglutide at week 60, both researchers and subjects remain blinded to medication condition during the re-randomized treatment period.

Figure 1. Subject flow through study.



¹ Estimated sample size for re-randomization at week 60 assumes an 18% attrition rate. All 120 enrolled participants will be considered part of the ITT sample for analyzes of treatment period outcomes at week 60.

Study Population:

State the following:

Subjects will be a total of 120 men and women, aged 18-70 years, with a BMI of 30 kg/m² or above (or ≥ 27 kg/m² with an obesity-related comorbidity).

Number of subjects to be studied: 120

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

Planned number of subjects to be treated in run-in period: N/A

Planned number of subjects to be randomized/started on study medication(s): 120 (3:2 semaglutide:placebo ratio, 72 taking semaglutide and 48 taking placebo for 60 weeks in Study 1; during the 12-week re-randomized treatment period in Study 2, a maximum of 14 will be assigned to semaglutide and 106 to placebo)

If multi-center trial: N/A

Anticipated number of trial sites: N/A

Anticipated number of subjects to be randomised/started on trial medication(s) at each trial site: N/A

Country(ies) planned to participate (if any): N/A

Inclusion Criteria

1. Men and women who report a desire to lose weight
2. Aged 18-70 years
3. Body mass index [BMI] ≥ 30 kg/m² or BMI ≥ 27 kg/m² with an obesity-related comorbidity (e.g., treated or untreated hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease)
4. Eligible female patients will be:
 - non-pregnant, evidenced by a negative urine pregnancy test
 - non-lactating
 - surgically sterile or postmenopausal, or they will agree to continue to use an accepted method of birth control during the study
5. Subjects must
 - Plan to remain in the Philadelphia area for the next 1.5 years.
6. Ability to provide informed consent before any trial-related activities.

Exclusion Criteria

1. A diagnosis of type I or II diabetes
2. Hemoglobin A1c (HbA1c) $> 6.5\%$
3. Uncontrolled hypertension (blood pressure $\geq 160/100$ mm Hg)

4. Clinically significant hepatic or renal disease
5. Uncontrolled thyroid disease
6. Experienced a cardiovascular event (e.g., stroke, myocardial infarction) in the last 6 months, congestive heart failure, or heart block greater than first degree
7. A history of acute pancreatitis in the last 6 months
8. Any history of chronic pancreatitis
9. A history of malignancy (other than non-melanoma skin cancer) within the last 5 years
10. A personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
11. A self-reported change in body weight >5kg (11 lbs) within 90 days before screening
12. Used within the last 6 months medications known to produce weight loss/gain (e.g., medications approved for weight loss, oral steroids, antipsychotic medications) or any GLP-1 receptor agonist.
13. Known or suspected allergy or hypersensitivity to trial medication(s), excipients, or related products
14. The receipt of any investigational drug within 6 months prior to this trial
15. Applicants with current severe major depressive disorder (BDI-II score ≥ 29 or Patient Health Questionnaire-9 [PHQ-9] score > 15) or severe anxiety disorder
16. Applicants with current, active suicidal ideation, and/or a suicide attempt within the past year (such individuals will be referred for psychiatric treatment if they have not previously received it).
17. Any severity of psychotic or bipolar disorder
18. Bulimia nervosa diagnosis within the past 5 years
19. Self-reported alcohol or substance abuse within the past 6 months, including at-risk drinking (current consumption of ≥ 14 alcoholic drinks per week)
20. History of (or plans to receive in the next 1.5 years) bariatric surgery or a weight loss device. (However, the following will be allowed: liposuction or abdominoplasty > 1 year before screening, laparoscopic banding if removed > 1 year before screening, intragastric balloon or aspire assist if removed > 1 year before screening.)
21. Inability to walk 5 blocks or more (comfortably) or engage in another form of aerobic activity.
22. Women who are nursing, pregnant, or planning to become pregnant in the next 1.5 years or are not using adequate contraceptive measures
23. Previous participation in this trial (e.g., randomized but failed to participate)
24. Changes to any chronic medication (type or dosage) within the past 3 months.
25. Food allergy or dietary preference that would prevent the individual from consuming the standard breakfast or ad libitum lunch.

Re-randomized Treatment Period Enrolment Criteria

1. To be eligible to participate in the re-randomized treatment period from weeks 60 to 72, subjects must also:
 - complete a week 60 assessment

- be classified as “on drug” as at the week 60 assessment and report taking at least one dose of trial product within the past 2 weeks

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 **Stopping Criteria** for individual subjects include:

1. The Principal Investigator and/or Physician Investigator conclude it is unsafe for the subject to continue.
2. A female subject becomes pregnant or reports the intention of becoming pregnant.

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

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

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

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

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

Protocol violation: The subject’s laboratory or other findings or conduct fail to meet the protocol entry criteria or fail to adhere to the protocol requirements. Use of medication(s)/treatment(s) not permitted during the trial would be considered a protocol violation.

Pregnancy or intention of becoming pregnant

Subject Replacement

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

Rationale for Study Population

The study population will be selected to be consistent with that for which the U.S. FDA approves subcutaneous semaglutide 2.4 mg. Additional exclusion criteria parallel those used in many clinical trials and include factors that may limit weight loss in the trial, such as a recent change >5kg in body weight, a history of bariatric surgery, or a weight loss device not removed > 1 year prior. Individuals with severe mental health symptoms, past 5 year bulimia nervosa, or current substance or alcohol abuse will be excluded, and those with current symptoms that are not being treated will be referred to appropriate treatments.

Only subjects who remain on drug at week 60 are included in Study 2, the re-randomized treatment trial, because this period is designed to test the effects of withdrawal from the study medication in a double-blinded fashion. The goals of Study 2 are thus not applicable to subjects who have already stopped taking the medication.

Visit Procedures

Screening procedures

Subjects will be recruited from the greater Philadelphia area via flyers and online, radio, and print advertisements. We also will advertise the study to patients who are treated at the 23 Penn-affiliated primary care practices. Phone screens will be conducted by trained staff to assess preliminary eligibility. Individuals who appear to be eligible will be invited for an in-person screening visit that includes: a behavioral evaluation conducted by a psychologist (including the principal investigator and co-investigator); informed consent; medical history; review of medications; blood draw; weight; height; and sitting blood pressure and pulse rate. For women of childbearing potential, a urine pregnancy test also will be performed.

Eligible subjects will sign informed consent prior to engaging in any study-related activity. As noted above, Study 1 and Study 2 will be described to subjects as two phases of the same 72-week trial. They will be told during initial consenting that only individuals who are taking the study medication will continue to participate after week 60 and that semaglutide-treated participants will be re-assigned at a 1:4 ratio to semaglutide or placebo at that time. Applicants will complete questionnaires that are administered as part of standard clinical practice at the Center for Weight and Eating Disorders: the Beck Depression Inventory-II (BDI-II) (44) to assess symptoms of depression; and the Weight and Lifestyle Inventory (WALI) (45) to provide information about the individual's weight history, prior weight-loss attempts, disordered eating behaviors, and other health behaviors (such as alcohol consumption). Applicants' responses to these questionnaires will be reviewed with the psychologist during the behavioral evaluation to assess initial eligibility.

Potentially eligible subjects will then provide a medical history and have a blood draw (to assess additional ineligibility criteria such presence of type 2 diabetes) and a urine pregnancy test (if applicable). Results of these tests will be reviewed by the study nurse practitioner or physician to determine whether the subject has any contraindications to weight loss or to the use of semaglutide, as detailed in the inclusion/exclusion criteria.

Study 1: Long-term treatment period randomization visit

Eligible subjects will then complete a baseline assessment of objective energy intake, subjective appetite, food reward, eating behavior, mood, and eating disorder symptoms. Subjects will complete this assessment individually and will not be assessed in groups. Self-report outcomes will either be completed online (using an e-mailed link) or using paper-and-pencil questionnaires (for those who prefer this method). Questionnaires will be reviewed for completeness during the in-person assessment visit, with any omissions or errors corrected.

After completing this assessment, subjects will be randomized in a 3:2 semaglutide:placebo ratio to placebo or semaglutide and will enroll in the 60-week lifestyle counseling intervention and will have their first lifestyle counseling session. Randomization will be accomplished using a computer-generated algorithm operated by the Investigational Drug Service (IDS) of the University of Pennsylvania. Assignment will be made from randomly permuted block sizes (5 or 10).

Additional assessments will occur at weeks 20, 40, and 60 (end of Study 1).

Study 2: Re-randomized treatment period

Subjects who complete a week-60 assessment and are taking the trial product at that time will be followed for an additional 12-week re-randomized treatment period. Eligible subjects (expected to be approximately 82% of those originally enrolled) who were originally assigned to semaglutide 2.4 mg will be re-randomized at week 60 (in a 1:4 semaglutide:placebo ratio) to receive either continued semaglutide 2.4 mg or placebo for 12 weeks. Re-randomization will be accomplished using a computer-generated algorithm operated by IDS. Only subjects originally assigned to semaglutide will be re-randomized. All of the subjects who were originally assigned to placebo will continue with that treatment from week 60 to week 72. Because re-assignment (or lack thereof) is operated by IDS, both researchers and subjects will continue to be blinded both to subjects' original treatment assignment and to their re-randomization assignment.

All subjects enrolled in the re-randomized treatment period will complete a final assessment and discontinue the trial product at week 72. They will return to clinic for a final off-medication safety visit at week 76.

933 Table 1. Schedule of study visits.

	Screen	Study 1: Long-term Treatment Study																	Study 2: Re-randomized Withdrawal Study			
Visit	0	1 R	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17 RR	18	19	20	21
Timing of visit (weeks)	-1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76
Visit window (days)	-14/+6		±7	-7/ +14	±1 4	±14	±14	-14/ +28	±14	±14	±14	±14	±28	±14	±14	±14	±14	±28	±14	±14	-14/ +21	±14
Information and Assessments																						
Informed consent	X																					
Behavioral evaluation	X																					
History and physical	X																					
Ad libitum energy intake		X						X					X					X			X	
Laboratory-based appetite ratings		X						X					X					X			X	
Global, past-week appetite and cravings (COEQ)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Implicit wanting and explicit liking of food (LFPT)		X						X					X					X			X	
Eating Disorder Examination		X						X					X					X			X	
Body weight (measured)	X	X		X	X		X	X	X		X		X		X		X	X	X	X	X	
Self-report weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Self-report questionnaires		X						X					X					X			X	
Trial product compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Treatment																						
Lifestyle intervention		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Trial product dose titration		X		X	X	X	X															
Trial product dispensing		X			X		X		X		X		X		X		X	X		X		
Safety																						
Adverse event reporting		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medical visit								X					X					X			X	

	Screen		Long-term Treatment Period																Re-randomized Period			
Visit	0	1 R	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17 RR	18	19	20	21
Timing of visit (weeks)	-1	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	56	64	68	72	76
Visit window (days)	-14/+6		±7	-7/ +14	±14	±14	±14	-14/ +28	±14	±14	±14	±14	±28	±14	±14	±14	±14	±28	±14	±14	-14/ +21	±14
Vital signs (WC, BP, HR)	X	X		X	X		X	X	X		X		X		X		X	X	X	X	X	X
Pregnancy test	X	X			X		X		X		X		X		X		X	X		X	X	
Blood draw	X							X					X					X				
CMP	X							X					X					X				
Lipids, HbA _{1c}	X																	X				
CSSRS	X							X					X					X			X	X

Note. R=randomization. RR=re-randomization (of semaglutide-treated subjects). COEQ = Control of Eating Questionnaire. LFPT = Leeds Food Preference Task. WC=waist circumference. BP=blood pressure. HR=heart rate. CMP = Comprehensive Metabolic Panel. CSSRS = Columbia Suicide Severity Rating Scale. Columns shaded in grey indicate principal outcome assessment visits.

Study 1: Lifestyle counseling intervention

Brief (15-minute) lifestyle counseling sessions will be delivered by a registered dietitian (or other trained health care provider) every 2 weeks from week 0 (i.e., baseline/randomization) to week 4 and every fourth week from week 5 to week 60 (17 total sessions) of Study 1. Subjects will be instructed to consume a self-selected diet of 1200-1500 kcal/day (for those who weigh < 250 lb) or 1500-1800 kcal/day (for those who weigh ≥250 lb). They will be instructed to engage in low-to-moderate intensity physical activity (e.g., walking), gradually building to a goal of ≥150 minutes per week (spread across 5 days) by week 36 and ≥225 minutes per week (spread across 5 days) by week 60. They will be instructed to use calorie counting and self-monitoring to meet their goals. This intervention will follow that used in the STEP-1 Program (1).

Makeup visits may be conducted either in-person or via telehealth (e.g. phone or videoconference). Telehealth also may be substituted for any non-assessment visit in order to maintain compliance with COVID-19 safety policies implemented at the university, state, or national level.

Study 1: Trial product interventions

In addition to the counseling sessions described above, subjects will take the trial product (semaglutide 2.4 mg or placebo), delivered once-weekly by self-administered, subcutaneous injection, beginning at the randomization visit (week 0).

Directions for Use (DFU) will be provided by Novo Nordisk global clinical supply. Subjects will be taught to administer the subcutaneous injection into their abdomen, thigh, or upper arm, and will be given written instructions for how to do so. To reduce the likelihood of gastrointestinal symptoms (e.g., nausea, vomiting), the trial product will be initiated at 0.25 mg and increased every 4 weeks (intermediate doses of .5 mg, 1.0 mg, and 1.7 mg) until a dosage of 2.4 mg is achieved at week 16. Subjects who do not tolerate an increased dose escalation will have a delayed escalation, and those unable to tolerate the 2.4 mg may continue to receive a lower dose at the investigators' discretion.

Subjects will be instructed to administer the trial product once weekly on the same day of the week (if possible) throughout the trial. Handling of missed doses will be consistent with the FDA-approved label for subcutaneous semaglutide 2.4 mg.

Study 2: Trial product interventions

Study 2 participants will continue to administer a trial product once weekly during the 12-week follow-up study. They will receive an 8-week supply of the trial product on one occasion and a 4-week supply on one occasion. No additional lifestyle counseling sessions are provided in Study 2.

Study 1: Assessments for efficacy

To calculate primary and secondary endpoints for Study 1, subjects will attend a 5-hour in-person assessment at weeks 0, 20, 40, and 60. They will be asked to fast for 12 hours (overnight) prior to their visit. They will be instructed to administer the medication on the

day of their usual scheduled dose and the date at which the medication was last administered will be recorded.

Subjects will complete all assessment-related activities, including consumption of the standardized breakfast and ad libitum lunch, individually in a private assessment space. We first will obtain duplicate anthropomorphic measurements, including weight (Detecto, model 6800A), height (with a wall-mounted stadiometer; Veeder-Root, Elizabethtown, NC), and blood pressure (Dinamap, model 9300). A fasting blood sample will be collected (safety assessment), and subjects will rate their fasting appetite using VAS scales (e.g., hunger, fullness, satiety, and prospective food consumption), as well as their level of thirst, nausea, and wellbeing (31, 32). They will then be asked to consume, in a 10-minute period, a standardized breakfast consisting of a liquid shake and conventional foods that provides a total of 550 kcal (approximately 15% protein, 30% fat, 55% carbohydrate) (9). VAS ratings of subjective appetite will be recorded at 30-minute intervals during the 4 hours after the breakfast meal.

Following this test, an ad libitum lunch, providing a variety of conventional foods, will be served in excess (8,9). Subjects' consumption of each food will be measured in grams, and meal duration and palatability ratings will be recorded. Total energy intake for the meal will be calculated based on the amount consumed of each food item.

Food reward (implicit food wanting and explicit liking) will be measured using the Leeds Food Preference Task (25, 26), an 8-minute computer task in which subjects are presented with common food items from four categories: high-fat sweet, high-fat non-sweet (savory), low-fat sweet, and low-fat non-sweet. To measure implicit food wanting, subjects are asked to respond quickly to forced choice pairings of each food paired with the foods in the other three categories (96 possible combinations). A frequency-weighted algorithm is used to account for both reaction time and selected preference. To measure explicit liking (exploratory outcome), subjects rate the pleasantness of tasting randomly presented images of each of the foods individually on a 100mm VAS scale.

The Eating Disorders Examination (EDE, 16th edition) (38) will be administered by a trained examiner. The binge eating section of the EDE will be used to assess frequency of objective and subjective binge episodes in the 28 days prior to each assessment visit. An objective binge episode refers to an individual's eating an objectively large amount of food (as judged by the examiner) and reporting loss of control over eating during the episode. A subjective binge episode refers to the individual's reported loss of control during an eating episode, despite the examiner's not judging the amount of food consumed to be objectively large. Both types of eating behavior are associated with self-recrimination, distress, and symptoms of depression. The EDE also yields four subscales rated on 7-point scales (0-6) with higher scores indicating greater pathology: Dietary Restraint, Eating Concern, Shape Concern, and Weight Concern. A Global EDE score is averaged across these four subscales.

All subjects will also complete self-report questionnaires that measure susceptibility to the rewarding properties of food (Power of Food Scale) (24), food cravings (Food Cravings Questionnaire-Trait) (34), cognitive restraint and dietary disinhibition (Eating Inventory) (35), weight-related self-efficacy (WEL) (36), mood (PHQ-9) (37), loss-of-control eating (LOCES) (39), and drive for thinness (EDI – Drive for Thinness) (40). Additional exploratory measures will include food addiction symptoms (Yale Food Addiction Scale) (41), body image satisfaction (Body Satisfaction Scale) (42), and weight-related self-stigmatization (Weight Bias Internalization Scale) (43). Additional questionnaires collected for exploratory analyses will include: the Body Appreciation Scale (54), Philadelphia Mindfulness Questionnaire (55), Paffenbarger Physical Activity Questionnaire (56), Impact of Weight on Quality of Life (57), Sleep Regulatory Questionnaire (58), and Perceived Stress Scale (59).

Measurements of body weight, waist circumference, blood pressure, pulse, and past-week appetite and cravings (COEQ) (8, 33) also will be collected at baseline, week 2, and every 4 weeks throughout Study 1.

Study 2: Assessments for efficacy

Subjects who enroll in Study 2 will be asked to complete an additional 5-hour assessment at cumulative week 72 that will include all of the same assessment procedures described above. Measurements of body weight, waist circumference, blood pressure, pulse, and past-week appetite and cravings (COEQ) (8, 33) will be collected every 4 weeks throughout Study 2.

Assessments for safety (Study 1 and Study 2)

Safety assessments include pulse, physical examination, adverse events (AEs), standard laboratory tests, and mental health/suicidal behavior, the latter as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) (45).

All information regarding adverse events will be actively collected from the point of the first study-related activity (i.e., completion of the informed consent procedure), through to each subject's study endpoint. This includes adverse events that may be related to any study procedure (i.e., laboratory tests) in addition to his/her use of the trial product. Side effects will be queried during every study visit, and the study nurse or physician will be available to assess the subject and evaluate and treat any adverse events.

Subjects in both groups also will have brief medical visits (10-15 minutes) occurring on 5 occasions throughout the 72-week trial (weeks 20, 40, 60, 72, and 76). These visits will check for possible complications of early weight loss and monitor response to the trial products. At each medical visit, subjects will be asked whether there has been any change in their health or medications. They also will be queried about their mood and suicidal ideation as determined by the C-SSRS. In the event of adverse mental health events, subjects will be referred to the study's psychologist or psychiatrist for

further evaluation, as appropriate. For all non-study-related medical events, subjects will be referred to their own primary care provider.

Subjects will have fasting blood draws (comprehensive metabolic panel [CMP]) at screening and weeks 20, 40, and 60. A lipid panel and HbA_{1c} also will be included at screening and week 60. Blood samples will be processed by Quest Diagnostics. Vital signs (blood pressure and pulse) will be measured at in-person clinic visits occurring every 4 weeks throughout Study 1 and Study 2, and at week 76. Female subjects who are of child-bearing potential will have a pregnancy test at screening and at weeks 0, 8, 16, 24, 32, 40, 48, 56, 60, 68, and 72.

Subject compliance

Throughout both studies, we will measure randomized subjects' medication adherence using injection counts from visual inspection of the dose counter taken from subjects' injection pens. Subjects 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. Subjects will be instructed to keep a medication diary, as part of their food and activity monitoring.

STATISTICAL CONSIDERATIONS:

Sample Size Calculation

Study 1

A power analysis was conducted for Study 1 for the primary outcome: ad libitum energy intake. Friedrichsen et al. (9) reported that reductions in energy intake from baseline to week 20 were 940 kJ ($SD = 889.1$; 225.0 ± 212.8 kcal) larger in the semaglutide 2.4 mg group than the placebo group, Cohen's $d = 1.06$. We considered the longer time frame of the present study (and that we are anticipating that effects sizes may decline over time) in selecting an estimated effect size of $d = 0.6$ for the difference between the groups in energy intake at week 60 (assuming larger effect sizes of 1.0 and 0.8 at weeks 20 and 40, respectively). We propose sequential testing of the week 20, 40, and 60 outcomes at $\alpha = .05$ to control for type 1 error. Based on data from similar studies conducted at our Center (e.g., (46)), we assumed a 10% attrition rate for the present study at week 60.

Based on these estimates, a baseline sample size of 120 subjects (72 assigned to semaglutide and 48 assigned to placebo) will give us 84% effective power (the product of marginal power for the preceding outcomes) to detect between-treatment group difference at week 60 of Study 1 as significant at $\alpha = 0.05$. The power analysis was conducted using G*Power 3.1.

Table 2. Marginal power and effective power for hierarchical testing of the three assessments of the primary outcome (energy intake) in Study 1.

Power analysis assumes an initial sample of 120 subjects allocated 3:2 to semaglutide or placebo with 10% attrition.

Order	Endpoint	Cohen's <i>d</i>	Marginal Power	Effective power
1	Energy intake at week 20	1.0	.99	.99
2	Energy intake at week 40	0.8	.98	.98
3	Energy intake at week 60	0.6	.86	.84

Study 2

As noted above, we currently lack pilot data with which to conduct a power analysis for the comparison of semaglutide-to-placebo and continuous-placebo groups in Study 2. We will use the present study to collect preliminary information that could be used in the future develop a fully powered non-inferiority trial.

In the present study design, we use an initial allocation ratio of 3:2 semaglutide vs placebo in Study 1 to ensure that there will be a sufficient number of semaglutide-treated patients at week 60 for re-randomization in Study 2. The 1:4 (semaglutide:placebo) re-randomization ratio used in Study 2 also is intended to preserve the size of the semaglutide-to-placebo group, because only semaglutide-to-placebo and continuous-placebo patients will be included in Study 2 statistical comparisons. (By re-allocating a small number of subjects to semaglutide-to-semaglutide at week 60, both researchers and subjects remain blinded to medication condition during the re-randomized treatment period.)

Statistical Methods

Analysis sets

Study 1 and Study 2 test different research questions and are based on slightly different samples (because only subjects on-drug at week 60 are eligible for Study 2). Thus, we plan to analyze and report the results of these two studies in two separate reports, referring to the results of Study 1 in reporting findings from Study 2. Data from both trials will be analyzed under the intention-to-treat (ITT) principle and will include all subjects who are randomized to a treatment condition.

In Study 1, the long-term treatment period (weeks 0 to 60), the ITT sample will include all 120 subjects who were randomized to semaglutide 2.4 mg or placebo, regardless of whether they continue taking the medication or complete a study assessment.

In Study 2, the re-randomized treatment period (weeks 60 to 72), the ITT sample will include all subjects (approximately 108) who complete a week-60 assessment, are classified as on drug at that time (by having self-administered the trial product in the prior 2 weeks), and receive trial product at week 60. Only the subjects assigned to continuous-placebo or semaglutide-to-placebo at week 60 are considered part of the primary comparison for Study 2. These subjects will be considered part of the Study 2

ITT sample regardless of whether they continue taking the medication or complete a week-72 study assessment.

Preliminary analyses

Data quality and integrity will be checked by assessing the data for missing and out-of-range values and univariate normality with basic statistical procedures, including descriptive statistics and visual graphical displays (e.g., histograms, scatter plots). For all analyses, residual analyses will be conducted to check for outliers, influential points, and violations in the normality assumption. If violations are detected, variance-stabilizing transformations will be considered.

A preliminary analysis of all outcome and baseline demographic variables will be performed to test for baseline differences between the randomized groups to determine adequacy of randomization. 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 sensitivity analyses will include the relevant variables as confounders in the primary and secondary analyses. Prior to the analysis of Study 2 data, we will repeat these steps in the subsample of participants who enroll in that trial.

Study 1: Long-term treatment period statistical analyses

Effects for Study 1, the long-term treatment trial, will be analyzed based on the ITT sample, as defined above. Analyses will be two-tailed and will be conducted using SPSS version 27.0 or R version 4.0. For all continuous outcomes (primary, secondary, exploratory), we will conduct ANCOVAs with change in the variable as the outcome, controlling for baseline values of the variable.

The primary outcome (ad libitum energy intake) and secondary confirmatory outcomes (laboratory-based and global subjective appetite, explicit responsiveness to the food environment, implicit food wanting) will be evaluated using a hierarchical testing procedure to control for type 1 error. We will first evaluate differences in the outcome at week 20 and will only proceed to test differences at week 40 and then week 60 if the earlier time points reach statistical significance at an alpha of 0.05. We chose to prioritize testing in this direction due to our previous study showing that the appetitive effect of liraglutide was strongest at the end of the dose titration period and attenuated gradually over time (10).

For global subjective appetite (COEQ), the week 20, 40, and 60 measures of hunger, fullness, and food preoccupation are considered to be secondary confirmatory endpoints and will be evaluated in this manner. Craving subscales assessed by the COEQ and by the General Food Craving Questionnaire (Trait) are considered secondary exploratory endpoints and will be evaluated as described below. We also will conduct exploratory comparisons of global appetite and cravings as measured by the COEQ at 4-week intervals throughout the trial in order to better characterize the timing of the medication's appetite effects. This will include COEQ measurements obtained prior to

week 20, between any significant endpoints, and between the last significant endpoint and the first non-significant endpoint (if applicable).

The treatment trial's supportive secondary endpoints (e.g., food cravings, eating behavior, mood, symptoms of disordered eating, body weight) and exploratory endpoints (e.g., food addiction, body dissatisfaction, weight-related self stigmatization) will be evaluated at weeks 20, 40, and 60 without the use of sequential testing. There is not sufficient prior evidence to support the hypothesis that the between-treatment difference in these outcomes will be largest early in treatment. Supportive secondary endpoints and exploratory endpoints therefore cannot be used to definitively determine treatment effects.

Study 2: Re-randomized treatment period statistical analyses

To evaluate the effect of withdrawing the medication on appetite, eating behavior, and psychosocial outcomes, we will compare differences at the week 72 endpoint between the semaglutide-to-placebo group and the continuous-placebo group. Differences between these two groups and the semaglutide-to-semaglutide group will not be subjected to statistical analysis (because the last group group is not relevant to determining whether participants who discontinue semaglutide differ from those who have not taken it).

Analyses will be based on the re-randomized treatment period ITT sample, as defined above. Analyses will be two-tailed and will be conducted using SPSS version 27.0 or R version 4.0. For all continuous outcomes, we will conduct ANCOVAs with the week-72 value as the outcome, controlling for the Study 1 baseline (week 0) values of the variable. Due to the separation of the aims and samples included in these two studies (including re-randomization of semaglutide-treated subjects), we will conduct these comparisons regardless of the statistical significance of the outcomes of Study 1. Further, due to the lack of pilot data on which to power these analyses, we will not control for multiple comparisons for the Study 2 analyses.

Missing data

The analyses described above will be conducted using imputed data sets. Estimated treatment differences and *SDs* will be pooled using Rubin's approach (47). Multiple imputation (MI) relies on the missing at random assumption. The number of iterations will be determined based on the fraction of missing data (48). Missing baseline values are expected to be minimal and will be estimated with a multiple imputation model including relevant demographic and outcome variables.

All available assessment data will be used regardless of whether the subject remains in treatment or on drug at the time of the assessment. For the primary ITT analyses (i.e., "treatment policy estimand") in Study 1, missing data in both groups will be imputed using data from the placebo group (including individuals who have discontinued treatment). This method is known as "jump to reference" multiple imputation (49) and makes the assumption that individuals in the semaglutide group who discontinue treatment will have an effect similar to the placebo group. The approach has

been used in several previous trials reported by Novo Nordisk (50, 51). When body weight is the primary outcome, the jump to reference approach is less conservative because it assumes that medication-treated individuals who discontinue treatment have a weight loss similar to treated individuals in the placebo group, and that placebo-treated individuals continue to receive the benefits of that treatment after discontinuation (52). However, with appetite outcomes, we do not expect large differences between individuals who are in treatment with placebo and those who are receiving no treatment at all. If sample size allows, we will evaluate this assumption by examining appetite outcomes in retrieved subjects who discontinued treatment.

A sensitivity analysis will be conducted using a traditional MI approach using treatment condition and relevant treatment and demographic variables as covariates, though we expect this estimate to be less conservative. If the number of retrieved subjects who have discontinued medication is large enough, we will conduct a sensitivity analysis in which the values of non-retrieved subjects are imputed using assessments from retrieved subjects within the treatment group, including timing of the last on-drug observation (52). Finally, we will conduct an exploratory subset analysis including only subjects who complete the study assessment and are on drug (defined as having taken a medication dose within 2 weeks) in order to characterize the size of the appetitive effects of semaglutide in those who adhere to that treatment.

For the Study 2 re-randomized treatment period, on the other hand, we believe that the assumption that semaglutide-to-placebo subjects who do not complete the week 72 assessment are similar to continuous-placebo subjects could obscure any differences that do occur between those groups. Therefore a standard multiple imputation approach, using treatment condition and relevant treatment and demographic variables as covariates, will be used to estimate any missing re-randomized treatment period (week 72) outcomes.

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

Not applicable

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

- 1294 • Who will use or disclose that information
1295 • The rights of research subjects to revoke their authorization for use of their PHI
1296 • View of PHI will be limited to individuals at the University of Pennsylvania
1297 directly involved in the study. The company donating the study product will not
1298 have access to PHI.
1299

1300 In the event that a subject revokes authorization to collect or use PHI, the investigator, by
1301 regulation, retains the ability to use all information collected prior to the revocation of
1302 subject authorization. For subjects who have revoked authorization to collect or use PHI,
1303 attempts will be made to obtain permission to collect at least vital status (i.e. that the
1304 subject is alive) at the end of their scheduled study period.
1305

1306 **Data Collection and Management**

1307 Subjects will be assigned an ID that will be used in all study communications.
1308 Research datasets will include only subject IDs, with a separate, password-protected
1309 dataset linking names and ID numbers. Study information will be stored electronically in
1310 a password-protected drive or secure data collection website (RedCap) or kept in locked
1311 files.

1312 All applicable national and international guidelines, regulations, and Institutional
1313 Review Board (IRB) guidelines regarding subject privacy and confidentiality will be
1314 followed throughout the study. These protections will apply to applicants being screened
1315 for study eligibility as well as to enrolled subjects. No identifying information will be
1316 included with stored research data, biological samples, clinical data, or reports of results.
1317 Penn network firewalls prevent unauthorized internal access to data, external access to
1318 data, and malicious intent to destroy data and systems. Controlled user access will ensure
1319 that only appropriate and authorized personnel are able to view, access, and modify study
1320 data. Data sent to the IRB, Investigational Drug Services, or the Safety Monitoring
1321 Committee will contain no identifying information, except as required when reporting
1322 AEs. Password-protected files linking subject names and ID numbers will only be
1323 accessible to the PI and research coordinator, and will be stored in a locked office.
1324 Information collected by the research team will not be placed in subjects' Electronic
1325 Medical Records (EMR).

1326 All research personnel will complete Penn's Collaborative Institutional Training
1327 Initiative (CITI) Protection of Human Subjects Research Training and HIPAA
1328 Compliance Training. Study staff involved in handling biological samples will complete
1329 additional IRB training in bloodborne pathogens.
1330

1331 **ETHICS:**

1332 The principal investigator (PI) will initiate and enroll subjects only after receiving IRB
1333 approval of the protocol and the informed consent documents. All recruiting materials
1334 used in the study will have IRB approval. Progress reports regarding the study will be
1335 submitted to the IRB in accordance with institutional and regulatory guidelines.
1336

1337 The study will be performed in compliance with the FDA Code of Federal
1338 Regulations for Good Clinical Practice (GCP). These procedures ensure the protection of
1339 the rights and the integrity of the subjects, adequate and correct conduct of all study
1340 procedures, adequate data collection, adequate documentation, and adequate data
1341 verification.

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

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

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

STUDY SCHEDULE:

The trial will take approximately 3 years to complete. Table 3 summarizes the proposed study timeline. Subjects will be recruited between months 3 and 17 and enrolled on a rolling basis at a rate of approximately two patients per week. The first subject's first visit will occur at month 3.5, and the last patient's last visit (week 76 safety visit) will occur at month 35. The integrated final study report will be completed in month 38.

Table 3. Study timeline

	Month						
	0	6	12	18	24	30	36, 38
Initial training and study start-up	X--X						
Recruitment (Month 3 – 17)	X-----X						
Long-term treatment period (Month 3.5 – 31)	X-----X						
Re-randomized treatment period/last safety visit (Month 17.5 – 35)				X-----X			
Data analysis and writing							X---X

STUDY DRUGS AND MATERIALS:

Study medication(s) / devices(s)

The pen injector is a 3 ml PDS290 pen-injector containing semaglutide 3.0 mg/ml or placebo solution for subcutaneous use.

The PDS290 pen-injector can dial 1-80 in increments of 1. The upscaling and dialed doses to use are described in the table below (4 weeks for each dose step until 2.4 mg, or “80” shown in dose counter, is reached).

Semaglutide dose	Value shown in dose counter
0.24 mg	8
0.5 mg	17
1.0 mg	34
1.7 mg	57
2.4 mg	80

Subjects who do not tolerate an increased dose escalation will have a delayed escalation, and those unable to tolerate the 2.4 mg dose may continue to receive a lower dose at the investigators' discretion.

All subjects assigned to semaglutide/semaglutide placebo will need 72 doses* of study medication. (*Some semaglutide-treated subjects will be switched to placebo for the last 12 weeks.)

Packaging and Labelling of Study Medication(s)

The medication will be provided by Novo Nordisk as ready-to-use, pre-filled pens in a subject box. Packaging and labeling will be done by Novo Nordisk according to annex 13 requirements.

Study drug will be shipped to the Investigational Drug Service at the University of Pennsylvania for assignment to research subjects per the randomization scheme.

Storage and Drug Accountability of Study Medication(s)

The trial medication will be refrigerated (36-46°F) (and the temperature will be checked daily.) The medications will not be frozen and will be protected from light. 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.

The research team will maintain adequate drug inventory and security at all times. Upon receipt of the study drug, the Investigational Drug Service 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 drug supplies will be kept in a secure, controlled enclosure with limited access, both at the Investigational Drug Service where the medication is received, and at the Center for Weight and Eating Disorders, where it will be dispensed to subjects. Access to the area in which medication is stored at the Center will be limited to the investigator and authorized staff. 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 to the

Investigational Drug Service, 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.

Randomization and Blinding

This is a 60-week double-blinded randomized treatment trial followed by a 12-week double-blinded discontinuation trial. Novo Nordisk Global Clinical Supply will not be responsible for managing the randomization of study subjects. Penn's Investigational Drug Service (IDS) will generate the initial randomization code using a 3:2 randomization scheme of semaglutide 2.4 mg to placebo. Assignment will be made from randomly permuted block sizes (5 or 10). The first subject to meet the randomization 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.

We will notify Penn's IDS when a subject who is on drug completes the week 60 assessment. For subjects originally randomized to semaglutide, IDS will reassign their medication condition using a 1:4 randomization scheme of semaglutide to placebo. Assignment will be made from randomly permuted block sizes (5 or 10) and will proceed in sequence as described above. Subjects originally assigned to placebo will not be re-randomized and will continue to receive placebo during the 12-week re-randomized treatment period. To maintain blinding, IDS will not inform the investigator of whether a particular subject is eligible for re-randomization.

Breaking of Blinded Codes

There is no planned breaking of the blinding during the trial period. The code for a particular subject may be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject or if demanded by the subject. Whenever a code is broken, the person breaking the code must record the time, date and reason as well as his/her initials in the source documents. All codes (whether broken or not) must be kept throughout the trial period. Accountability of all broken or unbroken codes (hard copy or electronic) will be performed at or after trial closure.

At the end of the trial, the investigator will provide the Novo Nordisk local safety department with a copy of the randomization list including subject identification number and trial product provided to each subject.

CONCOMITANT ILLNESSES AND MEDICATIONS:

Definitions:

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 subject'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:

We will comply with all local legal, regulatory, and IRB requirements in our reporting of 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 sponsor-investigator will be responsible for reporting all adverse events including serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSARs), serious adverse drug reactions (SADRs) (as defined below) to the Penn IRB. Information on all adverse events will be recorded in the source document and also in the appropriate adverse event module of the case report form (CRF). Information on study name, subject identification, event (i.e., diagnosis), drug, and reporter identification (e.g., name) will be collected and recorded in the source document (as detailed below). All serious adverse events and serious adverse drug reactions will be reported to the IRB within 24 hours.

The sponsor-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. Any other adverse events will be reported to Novo Nordisk at the same time as their submission to the Penn IRB or earlier.

The sponsor-investigator will collect the following information at minimum for each of these events:

1. Study name
2. Patient identification (e.g. initials, sex, age)
3. Event (preferably a diagnosis)
4. Drug (e.g. semaglutide)
5. Reporter identification (e.g., name, initials)
- 6) Causality, and 7) Outcome might be reported, if available.

Definitions

The PI and her investigative team acknowledge the definitions of the adverse events (AEs), serious adverse events (SAEs), and other untoward occurrences as spelled out below. The current version of the FDA approved Prescribing Information or any updates thereof will be used for assessment of expectedness.

Adverse event (AE):

An AE is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). This includes events reported from the first trial related activity after the subject has signed the informed consent and until post treatment

1504 follow-up period as defined in the protocol. The following should not be recorded as AEs,
1505 if recorded as medical history/concomitant illness on the CRF at screening:

- 1506 • Pre-planned procedure, unless the condition for which the procedure was planned has
1507 worsened from the first trial related activity after the subject has signed the informed
1508 consent
- 1509 • Pre-existing conditions found as a result of screening procedures

1510
1511 **Clinical laboratory adverse event:**

1512 A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically
1513 significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a
1514 severity, which requires active management, (i.e. change of dose, discontinuation of trial
1515 product, more frequent follow-up or diagnostic investigation).

1516
1517
1518 **Serious adverse event (SAE):**

1519 A serious AE is an experience that at any dose results in any of the following:

- 1520 • Death
- 1521 • A life-threatening* experience
- 1522 • In-patient hospitalisation or prolongation of existing hospitalization
- 1523 • A persistent or significant disability/incapacity
- 1524 • A congenital anomaly/birth defect
- 1525 • Important medical events that may not result in death, be life-threatening*, or require
1526 hospitalisation may be considered an SAE when, based upon appropriate medical
1527 judgement, they may jeopardise the subject and may require medical or surgical
1528 intervention to prevent one of the outcomes listed in this definition
- 1529 • Suspicion of transmission of infectious agents

1530 *The term life-threatening in the definition of SAE refers to an event in which the subject was at risk of
1531 death at the time of the event. It does not refer to an event which hypothetically might have caused death if
1532 it was more severe.

1533
1534 **Serious adverse drug reaction (SADR):**

1535 An adverse drug reaction (ADR) is an adverse event (AE) for which a causal relationship
1536 to the trial product is at least possible i.e. causal relationship is conceivable and cannot be
1537 dismissed. Serious adverse reaction (SAR): Adverse event which fulfils both the criteria
1538 for a Serious Adverse Event and the criteria for an Adverse Reaction.

1539
1540 **Suspected unexpected serious adverse reaction (SUSAR):**

1541 An SAE which is unexpected and regarded as possibly or probably related to the
1542 trial/study product by the investigator.

1543
1544 **Non-Serious adverse event:**

1545 A non-serious AE is any AE which does not fulfil the definition of an SAE.

1546
1547 **Severity assessment definitions:**

- 1548 • Mild: Transient symptoms, no interference with the subject's daily activities
- 1549 • Moderate: Marked symptoms, moderate interference with the subject's daily activities
- 1550 • 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

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 must be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the post-treatment follow-up period as stated in the protocol.

Follow-up of Adverse Events

During and following subjects' participation in the study, the sponsor-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. This medical care will be provided regardless of their insurance status. (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.)

All adverse events classified as serious or severe or possibly/probably related to the trial product will be followed until the subject has recovered and all queries have been resolved. For cases of chronic conditions, follow-up until the outcome category is "recovered" is not required, as these cases can be closed with an outcome of "recovering" or "not recovered". All other adverse events must be followed until the outcome of the event is "recovering" (for chronic conditions), or "recovered" or until the end of the post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved.

Pregnancy

Study subjects will be instructed to notify the sponsor-investigator immediately if they become pregnant. The sponsor-investigator will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by the sponsor-investigator will occur within the same timelines described above for reporting of Adverse Events.

Pregnancy itself is not considered to be an AE/SAE. Pregnancy complications will be recorded as adverse event(s) or serious adverse event(s), as appropriate. 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 semaglutide 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:

Subjects or observations 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. The PI will have final responsibility for determining which subjects or observations to exclude from the analysis. The subjects or observations to be excluded, and the reasons for their exclusion will be documented and signed by those responsible prior to database release. The documentation must be stored together with the remaining trial documentation.

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:

As noted above, the results of Study 1 and Study 2 are designed to be analyzed and published separately. 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., The Obesity Society, Society for the Study of Ingestive Behavior, The American Heart Association). We plan to publish the study results approximately 6 months after study completion.

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1636 The report of the primary outcome of Study 1 will be submitted to the New England
1637 Journal of Medicine. Study 2 will be submitted to the Lancet and secondary papers likely
1638 will be submitted to Obesity, International Journal of Obesity, or eating behavior
1639 journals.

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