Protocol: A Randomized Controlled Trial of Liraglutide 3.0 mg/d for Binge Eating Disorder

PI: KELLY C. ALLISON, PHD

VERSION 5.20.2019

A Randomized Controlled Trial of Liraglutide 3.0 mg/d for Binge Eating Disorder

INVESTIGATOR-INITIATED STUDY PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN): U1111-1172-4315

Department of Psychiatry

Perelman School of Medicine, University of Pennsylvania

3535 Market St # 3029

Philadelphia, PA 19104

Correspondence to:

Kelly C. Allison, Ph.D.
Director, Center for Weight and Eating Disorders
Perelman School of Medicine at the University of Pennsylvania
3535 Market St., Suite 3029
Phone: 215-898-2823, fax: 215-898-2878; kca@pennmedicine.upenn.edu

Table of Contents

BACKGROUND AND SIGNIFICANCE: 4

SPECIFIC OBJECTIVES: 6

PRIMARY OBJECTIVE 6

SECONDARY OBJECTIVES 6

RESEARCH DESIGN AND METHODS:..... 6

STUDY HYPOTHESES: 6

ENDPOINTS: 7

STUDY TYPE: 7

RATIONALE FOR STUDY DESIGN 8

STUDY POPULATION: 8

INCLUSION CRITERIA 9

EXCLUSION CRITERIA 9

RATIONALE FOR STUDY POPULATION 10

WITHDRAWAL CRITERIA 10

SUBJECT REPLACEMENT 11

VISIT PROCEDURES 11

FIGURE 1. STUDY FLOW DIAGRAM 12

SCREENING PROCEDURES 12

RUN-IN PERIOD 13

TABLE 1. SCHEDULE OF STUDY ASSESSMENTS AND LIFESTYLE INTERVENTION..... 15

RANDOMIZATION VISIT 16

FIGURE 2. DOSING SCHEDULE FOR LIRAGLUTIDE 16

MEDICAL ASSESSMENT..... 17

ASSESSMENTS FOR EFFICACY 17

ASSESSMENTS FOR SAFETY 18

SUBJECT COMPLIANCE 18

ASSESSING ADVERSE EVENTS.....18

STATISTICAL CONSIDERATIONS: 19

SAMPLE SIZE CALCULATION 19

STATISTICAL METHODS 19

DATA HANDLING AND RECORD KEEPING: 2

ETHICS: 20

STUDY SCHEDULE: 21

STUDY DRUGS AND MATERIALS: 22

STUDY MEDICATION 22

PACKAGING AND LABELLING OF STUDY MEDICATION 22

STORAGE AND DRUG ACCOUNTABILITY OF STUDY MEDICATION 22

RANDOMIZATION AND BLINDING 23

BREAKING OF BLINDED CODES 23

CONCOMITANT ILLNESSES AND MEDICATIONS: 23

ADVERSE EVENTS: 24

LIABILITY AND SUBJECT INSURANCE: 26

EVALUABILITY OF SUBJECTS: 26

PREMATURE TERMINATION OF STUDY: 27

PUBLICATION PLAN: 27

REFERENCES: 28

BACKGROUND AND SIGNIFICANCE:

Binge eating disorder (BED) was first described in 1959 by the founder of our Center for Weight and Eating Disorders, Dr. Stunkard [1], who, along with Co-I Dr. Wadden, was involved in establishing the first diagnostic criteria for BED [2]. BED is a serious psychiatric condition that often co-occurs with mood, anxiety, and/or substance abuse disorders [3,4]. In the Diagnostic and Statistical Manual 5 (DSM 5)[5], the Feeding and Eating Disorders section has been revised and expanded. BED previously was categorized under eating disorder not otherwise specified (ED-NOS), but is now a stand-alone disorder. With this new recognition, it is likely that more patients will be seeking treatment, and, consequently, more healthcare providers will need efficacious treatments for BED.

BED is characterized by the consumption of an objectively large amount of food in a short period (≤ 2 hours), accompanied by feeling a loss of control over eating [5]. Persons typically eat more rapidly than usual, eat until uncomfortably full, eat large amounts when not physically hungry, eat alone due to embarrassment, and feel disgust or upset about these episodes after they occur. Binge episodes must occur once per week for an average of 3 months for a diagnosis of BED. The prevalence of BED in the general population is 1.6% of women and 0.8% of men, based on DSM-IV criteria [6], but these numbers will likely increase given the decreased threshold to one binge episode required per week (as compared to the previous criteria of two episodes per week). For example, a recent study of a representative sample of Australian late adolescents and adults reported a prevalence range of 5.6 – 6.9% for BED using the DSM 5 diagnosis [7]. The prevalence also increases as body mass index (BMI) increases including persons seeking weight loss treatment [8] and those seeking bariatric surgery [e.g., 9]. BED is also associated with significant health complications independent of BMI, including increased risk for chronic neck and back pain, diabetes, hypertension, and chronic headaches [10].

As stated above, persons with BED are more likely to have co-morbid psychiatric diagnoses, such as mood disorders, anxiety disorders, and substance use disorders as compared to persons without an eating disorder [4]. A recently published meta-analysis has also confirmed that quality of life is significantly lower among individuals with BED as compared to those without it [11]. Treatment for BED often improves co-morbid mood and anxiety symptoms, as well as quality of life [12].

Aside from the core behavior of engaging in binge episodes, BED is associated with a range of eating disordered attitudes and behaviors. Previous studies have established that persons with BED experience higher levels of disinhibition over eating and perceived hunger [13]. In addition, food cravings are often extreme among those with BED, typically described as experiencing obsessions with food and feeling compelled to act on those thoughts. Thus, these extreme thoughts regarding food interfere with one's ability to resist binge episodes. Successful treatment of BED should help improve these psychological correlates of disordered eating behavior, as well as reduce the actual occurrence of binge episodes. However, data regarding the impact of liraglutide has not been published (to our knowledge) that demonstrate its impact on these psychological factors related to eating behavior.

Lisdexamfetamine is the only medication currently approved by the FDA for the treatment of BED [14], although other medications, including selective serotonin re-uptake inhibitors (SSRIs)

[15-16], topirimate [17], and sibutramine [18] have been tested for this disorder. McElroy and colleagues tested several dosing levels of lisdexamfetamine as compared to placebo, using a 3-week titration period and 8 week trial at full strength. They found reductions in the frequency of binge episodes per week for placebo and the 30-, 50-, and 70-mg/d treatment groups of [mean (SD)] -3.3 (2.04), -3.5 (1.95), -4.1 (1.52), and -4.1 (1.57), respectively. These reductions were significantly greater in the 50- and 70-mg/d groups as compared to placebo. The percentage of participants who achieved cessation from binge episodes for four weeks at the end of the trial was 42% of those on placebo vs. 50% across all treatment groups. Reductions in body weight were -0.1 (3.09), -3.1 (3.64), -4.9 (4.43), and -4.9 (3.93) kg for placebo, and the 30-, 50-, and 70-mg/d groups, respectively. (All treatment groups differed significantly from the placebo group.)

Examining the effects of a weight loss agent, sibutramine (15 mg/d), as compared to placebo over 24 weeks, Wilfley et al. showed significant reductions in binge episodes per week among those taking sibutramine, with a mean (SD) of -2.7 (1.7) as compared to -2.0 (2.3) for those on placebo [18]. (Our study physician, Dr. Berkowitz was an investigator for this trial.) Of those on sibutramine, 58.7% achieved cessation of binge episodes for four weeks as compared to 42.8% of the placebo group. Weight loss was also significantly greater in the sibutramine group with a mean (SD) = - 4.3 (4.8) kg as compared to that with placebo, +0.8 (3.5) kg.

However, sibutramine is no longer available on the market in Europe or the United States due to medical complications. Randomized controlled trials of some SSRIs have shown significant reductions in binge episodes per week as compared to placebo, but weight loss has not generally been significant or long-lasting on these agents. In addition, sexual functioning is often adversely impacted on SSRI agents. While topiramate has shown successful reductions in both binge episodes and weight [17], its side effect profile, particularly its negative effect on cognitive functioning, often makes this medication difficult to tolerate. Thus, more medications are needed that produce significant reductions in binge eating, as well as weight, among this population.

In sum, BED is a serious disorder associated with distress and medical co-morbidities. Cognitive behavior therapy is considered the most effective treatment for BED [19], but it is expensive, time-consuming, and not available in many geographical regions. Thus, effective pharmacotherapies are needed for this patient population, particularly medications that do not increase weight or negatively affect sexual functioning, as found with SSRIs, or cognitive functioning, as often seen with topiramate. Finally, as a stimulant, lisdexamfetamine poses the potential for abuse, which may be problematic for a significant proportion of persons with BED, given the elevated rate of substance use disorders among persons with BED [3,4].

The proposed study will test the efficacy of liraglutide 3.0 mg/d (Saxenda) for the treatment of BED. Although data do not seem available regarding liraglutide's effect on dampening the drive to eat in previously published weight loss trials [20, 21], there is some evidence that liraglutide could help significantly reduce the urge to engage in binge eating, and also suppress appetite. Only one previous study has tested liraglutide in the treatment of BED, to our knowledge [22]. This study was an open-label administration of liraglutide 1.8 mg/d with minimal diet and lifestyle advice, as compared to diet and lifestyle advice only among patients in Malaysia. BED symptoms were assessed with the self-reported Binge Eating Scale (BES) [23]. Participants assigned to liraglutide significantly decreased their BES scores at 6 and 12 weeks (study end).

These participants also showed significant decreases in weight (95.5 to 90.1 kg), waist circumference, systolic blood pressure, fasting glucose, and total cholesterol. However, there were several weaknesses with this study, including its lack of a placebo group and its reliance on a global self-report measure of binge eating, as compared to specific assessment of the frequency of binge episodes per week. As such, a randomized controlled trial (RCT) would be a logical next step to test whether liraglutide 3.0 mg/d is superior to placebo.

SPECIFIC OBJECTIVES:

Primary Objective:
To test the efficacy of liraglutide 3.0 mg/d as compared to placebo in reducing the number of binge episodes per week during a 17-week, randomized, placebo-controlled trial.

Secondary Objectives:
To compare the proportion of participants on liraglutide 3.0 mg/d as compared to placebo who achieve remission from binge episodes at week 17, defined as having no binge episodes for the previous 4 weeks.

To compare differences between the liraglutide 3.0 mg/d and placebo groups in changes in body weight, global BED symptom improvement, cognitive restraint of food intake, dietary disinhibition, perceived hunger, quality of life, and depressed mood at treatment end.

Of note: the Eating Inventory (cognitive restraint of food intake, dietary disinhibition, and perceived hunger) was administered at baseline and at study end. With the small number of completers, it may not be possible to run the mixed models analyses on these outcome variables.

RESEARCH DESIGN AND METHODS

Study Hypothesis (hypotheses):

The trial has the following **primary aim and hypothesis**:
Aim 1. The primary aim is to test the efficacy of liraglutide 3.0 mg/d in reducing the number of binge episodes per week during a 17-week, randomized, placebo-controlled trial.

H_1: We hypothesize that participants randomized to liraglutide 3.0 mg/d (n =76) will show significantly greater reductions in the number of binge episodes per week as compared to those on placebo (n = 76).

Of note, the final sample size is n=36 total.

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

Aim 2. We will compare the proportion of participants in the two groups who achieve remission from binge eating at week 17, defined as having no binge episodes for the previous 4 weeks.

H_2: We hypothesize that significantly more participants in the liraglutide 3.0 mg/d group will achieve remission at week 17 as compared to the placebo group.

Aim 3. We will compare differences between the liraglutide 3.0 mg/d and placebo groups in changes in body weight, global improvement BED symptom improvement, cognitive restraint of food intake, dietary disinhibition, perceived hunger, quality of life, and depressed mood at week 17.

H_3: We hypothesize that participants randomized to liraglutide 3.0 mg/d as compared to those assigned to placebo, will lose significantly more weight, and show greater improvements in investigator-rated global BED symptoms, cognitive restraint of food intake, dietary disinhibition, hunger, quality of life, and depressed mood. (We note that these latter comparisons, Aims 2 and 3, are considered exploratory. The study is not powered to determine significant differences among groups on these outcomes.)

We note that the Eating Inventory subscales (restraint, disinhibition, and hunger) were completed at baseline and treatment end only, and we may not have enough completers to run the final analyses for this secondary outcome.

Endpoints:

Primary

The primary endpoint is change in binge episodes per week from randomization (week 0) to study end (week 17).

Secondary

The secondary endpoints include examining the proportion of participants who have achieved remission from binge-eating (no binge episodes between weeks 13 – 17), week 17 rating on the interviewer-based Clinical Global Impression of Improvement Scale (CGI-I)[24] for global assessment of BED symptoms, and changes in body weight, cognitive restraint of food intake, dietary disinhibition, perceived hunger, quality of life, and depressed mood.

(See note above regarding restraint, disinhibition, and hunger variables.)

Study type:

We propose a 17-week, single-center, double-blind, randomized placebo-controlled trial with parallel groups. There are two treatment arms: a) liraglutide titrated over 5 weeks to 3.0 mg/d, followed by 12 weeks on full dose, and b) placebo for the full 17 weeks. Seventy-six participants will be randomized to each of the two groups, for a total of 152 participants with BED.

Of note, the final sample size for analyses will be 36 participants.

Rationale for Study Design

We have considered the design of this study at length based on the literature and our group's experience with clinical trials for BED [e.g. 18, 25]. Most previous RCTs for BED, and certainly all of the initial trials for each individual agent, have used a simple double-blind, randomized placebo control design to demonstrate efficacy [see 26 for review]. Cross-over designs have not been used in any of these trials to date. As reviewed above, only one open label trial of liraglutide 1.8 mg/d has been published [22], so this would be the first placebo-controlled trial testing the efficacy of liraglutide for BED.

Of note, previous studies have shown 30 – 60% of persons with BED are responsive to placebo. Those with mild symptom profiles tend to be most susceptible to placebo response [27]. Therefore, many BED trials include a run-in period [28-30], typically for a duration of 1-4 weeks, where participants self-monitor their binge episode frequencies or are administered placebo in a single-blind fashion. If participants' binge episodes persist over the course of this run-in period, they have demonstrated stability of symptoms and are typically less responsive to placebo [27]. We plan to use a 2-week run-in period consisting of daily monitoring of binge episodes in the proposed study to ensure the stability of BED in our participants. Participants will not be using a placebo during this run-in. After this run-in period, we will use a 17-week double-blind placebo-controlled trial to test the efficacy of liraglutide compared to placebo in reducing binge eating episodes, along with our secondary outcomes. The 17-week duration will allow for titration to the 3.0 mg dose over 5 weeks, followed by a 12 week trial at the full dose, which would allow for adequate time to test for efficacy of the medication on reduction in BED symptoms. This duration is longer than the trial of 11-weeks (3-week titration, 8 week full dose) for lisdexamfetamine [14] and the Malaysian group's 12-week (total) trial of liraglutide [23].

Study population:

We will randomly assign 152 participants with BED to either placebo or liraglutide 3.0 mg/d (Saxenda) for the first phase of the trial. We expect to screen about 500 persons by phone. Of these, we expect 220 to attend the screening visit. We expect about a third of these to not meet criteria for BED after the 2-week run-in period, leaving 152 to be randomized to start the intervention (medication or placebo). We will recruit these participants at a single site – the Center for Weight and Eating Disorders at the University of Pennsylvania, Philadelphia, PA, USA - through local media advertisements and news shows/outlets, as well as Internet-based advertising outlets and flyers around our community. We will be utilizing the university-based website iConnect, which allows access to their volunteer registry data of interested research volunteers. We have extensive experience recruiting for studies of BED and other forms of disordered eating, and believe that enrolling 152 participants with BED over the course of 36 months is highly feasible.

UPDATE: We received 1,016 contacts for screening and completed 305 phone screens. However, we were only able to randomize 36 participants who entered the study successfully. (We randomized 37, but one participant told us after starting the protocol that she was already taking metformin, an exclusion criteria, so she was censored).

Inclusion Criteria

1. BMI > 30 kg/m^2 or BMI ≥ 27 - 29.9 kg/m^2 in the presence of at least one weight-related comorbid condition, such as binge eating disorder, hypertension, or dyslipidemia. There is no upper BMI limit for this trial.
2. Age ≥ 21 years and ≤ 70 years
3. Meet full DSM 5 criteria for BED
    a. Recurrent episodes of binge eating characterized by both consuming an abnormally large amount of food in a short period of time compared with what others might eat in the same amount of time under the same or similar circumstances and experiencing a loss of control over eating during the episode.
    b. These episodes feature at least 3 of the following:
        i. consuming food more rapidly than normal;
        ii. eating until uncomfortably full;
        iii. consuming large amounts of food when not hungry;
        iv. consuming food alone due to embarrassment;
        v. feeling disgusted, depressed, or guilty after eating a large amount of food.
    c. Significant distress about the binge episodes is present.
    d. Binge episodes must occur, on average, at least once per week for 3 months.
4. All races and ethnicities are included
5. Eligible female subjects will be:
    - non-pregnant, evidenced by a negative urine dipstick pregnancy test
    - non-lactating
    - surgically sterile or postmenopausal, or they will agree to continue to use an accepted method of birth control during the study
6. Ability to provide informed consent before any trial-related activities
7. Subjects must:
    - have a primary care provider (PCP) who is responsible for providing routine care
    - have reliable telephone or Internet service to communicate with study staff
    - understand and be willing to comply with all study-related procedures and agree to participate in the study by giving written informed consent
    - plan to remain in the Philadelphia area for the next 6 months or more

Exclusion Criteria

1. Pregnant or nursing, or plans to become pregnant in the next 6 months, or not using adequate contraceptive measures
2. Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
3. Uncontrolled hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg)
4. Type 1 diabetes
5. Type 2 diabetes
6. A combination of fasting glucose ≥ 126 mg/dl, combined with an HbA1c >6.5, will be used to indicate the presence of diabetes, an exclusion criterion
7. Recent history of cardiovascular disease (e.g., myocardial infarction or stroke within the past 6 months), congestive heart failure, or heart block greater than first degree
8. Clinically significant hepatic or renal disease

9. Thyroid disease, not controlled
10. History of malignancy (except for non-melanoma skin cancer) in past 5 years
11. The presence of current anorexia nervosa or bulimia nervosa
12. Current major depressive episode, active suicidal ideation, or history of suicide attempts within the past 5 years. We will exclude participants who have a Patient Health Questionnaire-9 (PHQ-9) [31] score > 15, or a score of $\geq$ 1 on the suicidal ideation item, as well as any risk of suicidality as measured by a score of 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS)[32].
13. Psychiatric hospitalization within the past 6 months
14. Self-reported alcohol or substance abuse within the past 12 months, including at-risk drinking (current consumption of $\geq$ 14 alcoholic drinks per week)
15. Current or past psychosis
16. Use in past 3 months of medications known to treat BED (such as lisdexamfetamine), induce significant weight loss (i.e., prescription weight loss medications), or induce weight gain (e.g., chronic use of oral steroids, second generation antipsychotics)
17. Currently receiving behavioral or pharmacological treatment for BED
18. Loss of $\geq$ 10 lb of body weight within the past 3 months
19. Known or suspected allergy to trial medication(s), excipients, or related products
20. Hypersensitivity to liraglutide or any product components
21. The receipt of any investigational drug within 6 months prior to this trial
22. Previous participation in this trial (e.g., randomized and failed to participate)
23. History of pancreatitis
24. History of gastrointestinal surgery (With the exception of individuals who have previously had an adjustable gastric band but subsequently have had it removed at least six months prior to the study. These individuals would not be excluded).

Rationale for Study Population

Exclusion criteria include children or adolescents, as liraglutide is not indicated for use in these groups. Persons older than 70 years will be excluded as little is known about the occurrence of BED in this age group. BMI criteria will be set at $\geq$ 27 kg/m^2 to capture overweight and obese patients with BED. Given that BED confers medical risks independent of BMI, we propose including BED as a co-morbidity that would qualify those with a BMI between 27 – 29.9 kg/m^2 for treatment. Persons with BED who also have diabetes will be excluded as diabetes can independently influence the timing and degree of food intake. In this first trial, we would like to examine the impact of liraglutide on BED independently of any effects of medical conditions on eating. Similarly, we would like to focus on the effect of liraglutide on BED symptoms, so we will exclude persons with other significant psychiatric diagnoses, as listed above. We will exclude participants who have a Patient Health Questionnaire-9 (PHQ-9) [31] score > 15, or a score of $\geq$ 1 on the suicidal ideation item, as well as any risk of suicidality as measured by a score of 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS)[32]. We also would like to study persons free of diabetes and without any other uncontrolled significant medical problems that could influence their eating patterns and outcomes. Those who are currently receiving weight loss or BED treatment, or have taken medications for weight loss or BED treatment in the past 3 months will be excluded as we would like to examine the impact on BED independently of any other treatments that may affect the study outcomes. Finally, we will exclude persons who have had previous gastrointestinal surgery, including sleeve gastrectomy,

gastric bypass, or an adjustable gastric band, as these surgeries affect the amount of food that can be consumed at one sitting.

Withdrawal Criteria

A subject may voluntarily withdraw from the study at any time for any reason. The sponsor-investigator, Dr. Allison, also may withdraw the subject from further participation at any time, if it is considered in the best interest of the subject or the study, without prejudice to the subject's future medical care.

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

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

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

Lost to follow-up: In the case of subjects who do not return to the center for study procedures and cannot be contacted, study personnel will make vigorous and repeated attempts (minimum of 3) to contact the subject. These attempts will include at least 1 certified mail receipt. If all attempts to contact the subject fail, that subject will be considered to be lost to follow-up and discontinued from the study.

Protocol violation: The subject's laboratory or other findings, or the subject's conduct, fail to meet the protocol entry criteria or fail to adhere to the protocol requirements. Subject pregnancy or intention of becoming pregnant would also be a violation.

The Stopping Criteria for individual subjects include:

The Principal Investigator, study physician, and/or nurse practitioner conclude it is unsafe for the subject to continue. These reasons may include:

- A new diagnosis is made of a significant medical condition which could influence the response to liraglutide (e.g., renal failure).
- A medication is begun that could alter the subject's responses to liraglutide.

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

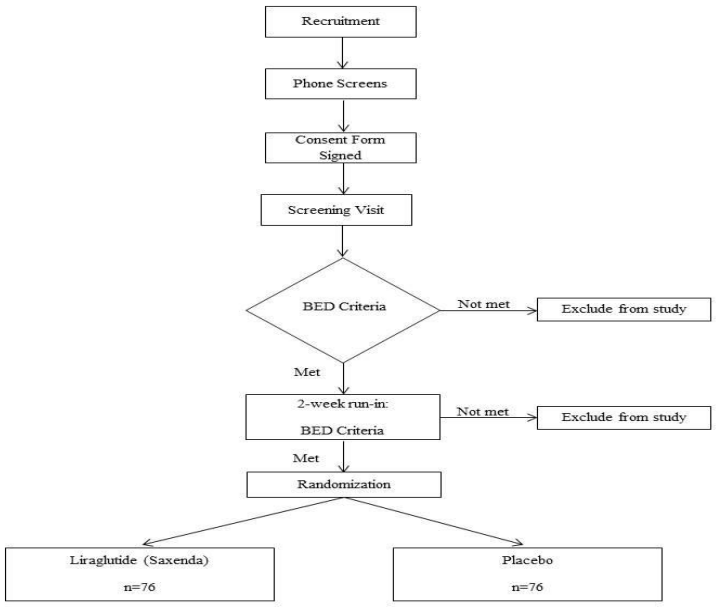
Subject Replacement

Subjects who prematurely discontinue from the study or become ineligible will not be replaced once they have been randomized.

Visit Procedures

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

Figure 1. Study Flow Diagram



Screening Procedures

All applicants will be screened by phone and questions administered through REDCap (the University of Pennsylvania's research data capture system) to determine whether they potentially meet eligibility criteria. We will obtain a waiver of written documentation of consent for the telephone and electronic questionnaire screen. Those who appear to meet eligibility criteria and remain interested in the trial will be scheduled for an in-person interview.

The in-person interview will be conducted by a psychologist or Masters' level staff member, who will obtain informed consent and evaluate subjects' behavioral eligibility (i.e., willingness and appropriateness to participate). Individuals who do not wish to participate in the research study will receive recommendations for alternative treatments for binge eating disorder if they are interested. Assessment of eligibility will include examination of the applicants' BED symptoms, as measured by the Eating Disorder Examination (interview version, 16th edition) [33], their mood (using a cut score of 15 on the PHQ-9)[31], suicidality (including history of suicidal ideation and behavior), as assessed at screening by a score of 4 or 5 on the Columbia-Suicide Severity Rating Scale [32]), and other general psychopathology, as measured by the Mini International Neuropsychiatric Interview 7.0 (MINI) [34]. Participants will be asked to complete additional questionnaires including the Eating Inventory (EI) [35], a questionnaire assessing demographic characteristics, Loss of Control Eating Scale (LOCES) [36] to measure frequency of specific eating behaviors related to loss of control, Yale Food Addiction Scale [37] to identify those most likely to be at risk for substance dependence with the consumption of high

fat/sugar foods, Toronto Alexithymia Scale (TAS-20) [38] as a self-report measure of features associated with Alexithymia, Night Eating Questionnaire (NEQ) [39] to assess the behavioural and psychological symptoms of night eating syndrome, Pittsburgh Sleep Quality Index (PSQI) [40] to measure sleep patterns and sleep quality, the Food Craving Questionnaire – State (FCQ-S) [41] and the Food Craving Questionnaire – Trait (FCQ-T) [41] to assess state and trait attitudes towards food cravings.

The Eating Disorders Examination (EDE, 16th edition) [33] is a standardized interview devised for the assessment of the psychopathology specific to eating disorders. It is considered the gold standard for assessment of BED. Specifically, the EDE assesses the frequency of different forms of overeating during the previous 28 days, including objective binge episodes (i.e., consuming unusually large quantities of food with a subjective loss of control), subjective binge episodes (i.e., subjective loss of control while eating a quantity of food not judged to be large given the context) and objective overeating episodes (overeating without a loss of control). It also assesses inappropriate compensatory behaviors that have occurred in the previous 28 days associated with eating disorder psychopathology. The EDE 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. The EDE will be administered by a trained rater at baseline and week 17. It takes approximately an hour to administer. The binge eating section of the EDE will be used to assess frequency of binge episodes at each medical visit.

The Eating Inventory (also known as the Three Factor Eating Questionnaire) consists of 51 items that assess three factors: Cognitive Restraint, Disinhibition, and Hunger [35]. Scores increase positively with endorsement of items for each factor. Higher disinhibition scores have been linked to greater frequency of binge eating, while higher cognitive restraint and lower hunger scores are associated with larger weight losses among overweight persons in weight loss programs. The Eating Inventory will be administered at baseline and week 17.

The MINI 7.0 [34] assesses most Axis I disorders, such as major depressive disorder, bipolar disorder, the anxiety disorders, attention deficit-hyperactivity disorder, and psychosis. It will be used to characterize the sample and to identify psychiatric conditions that are listed as exclusions to participation. The MINI will be administered at baseline and takes approximately 15-25 minutes.

Subjects who remain interested and pass this portion of the assessment will proceed to meet with the study physician or nurse practitioner, who will obtain a medical history and conduct a physical examination to determine medical eligibility. Persons who continue to remain eligible will proceed to have an electrocardiogram (EKG) and fasting blood test to determine that final eligibility criteria are met. As detailed below, safety screening labs include a comprehensive metabolic panel (including glucose), lipids, hemoglobin A1c, and a urine pregnancy test (for females of child-bearing age). These labs will be repeated at week 17.

The following procedures will be completed at the screening visit as discussed above: informed consent; behavioral evaluations; assessment of criteria for BED; medical history; full physical exam; review of medication; 12-lead EKG; blood draw (approximately 1 tablespoon - i.e., 15 ml

of blood); weight; height; and sitting blood pressure and pulse rate. For women of childbearing potential, a urine pregnancy test also will be performed. Results of these tests will be reviewed by the study physician or nurse practitioner to determine whether the subject has any contraindications to the use of liraglutide, as detailed in the inclusion/exclusion criteria.

Run-In Period

Upon successful completion of the screening visit, subjects will be asked to not change anything and eat as they normally would for 2 weeks. Once per week over these two weeks they will receive a brief survey through REDcap to assess their binge eating episodes. For those without internet access, study staff will call the participant to ask this information over the phone. If participants report having at least one binge episode per week (a total of two or more during the two weeks), they will be included in the trial. Subjects will be trained at the screening visit on general guidelines for the definition of a binge episode.

Table 1. Timeline and Procedures

	Screening		RCT									
	Weeks											
	Screen	2-week run-in	Randomization/ Week 0	1	3	5	7	9	11	13	15	17
Procedures												
Informed consent	x											
Adverse events actively collected	x	x	x	x	x	x	x	x	x	x	x	x
Behavioral evaluation	x											
History and physical	x											
EKG	x											
Blood draw	x											x
Labs	x											x
Log of BED behaviors		x										
Self-reported outcomes			x	x	x	x	x	x	x	x	x	x
Medical visit			x	x	x	x	x	x	x	x	x	x
Psychological assessment of BED symptoms	x		x	x	x	x	x	x	x	x	x	x
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x

Note: Shaded weeks are formal assessment weeks. Data regarding binge episodes, weight, vital signs, mood and suicide risk, and other self-reported outcomes will be collected at each medication visit, as well.

Randomization Visit

Subjects who continue to meet eligibility criteria assessed at the screening visit and during the run-in period will be scheduled for a randomization visit at the Center within 3 weeks of their screening.

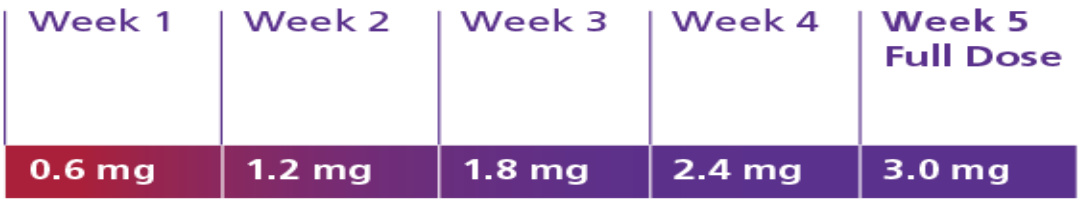
Subjects will be randomly assigned to the two interventions in equal numbers (i.e., 1:1 ratio). This will be accomplished using a computer-generated algorithm operated by the Investigational Drug Service of the University of Pennsylvania. Assignment will be made from randomly varied block sizes (2, 4, or 6), realizing that this method may require slightly more than 152 participants to be randomized in order to achieve perfect balance between the two groups.

The subject's weight, blood pressure, and pulse will then be measured, following the methods described later (see Assessment for Efficacy).

Following randomization, all subjects will have a medical visit with the study physician or nurse practitioner who will instruct them in the use of liraglutide 3.0 (as described later) and provide the first month's supply of medication.

Subjects will be provided liraglutide 3.0 (Saxenda) or placebo after being randomized at week 0. Liraglutide 3.0, a glucagonlike peptide-1 receptor agonist, is a once-daily self-administered, subcutaneous injection [42]. Liraglutide 3.0 mg or placebo will be provided as pre-filled, disposable, personal injectors. Subjects will be taught (by the study physician or nurse practitioner) how to properly perform subcutaneous injections into their abdomen, thigh, or upper arm. In addition, subjects will be given an instruction card about how to administer the medication. To reduce the likelihood of gastrointestinal symptoms (e.g., nausea, vomiting), the medication will be initiated at 0.6 mg daily for 1 week, and then increased by 0.6 mg/day in weekly intervals until a dose of 3 mg/day is achieved (please see below for dosing schedule). Subjects will be instructed that if they miss a dose, to resume the once-daily regimen with the next scheduled dose and not to take an extra dose or higher dose. If subjects miss more than 3 days, they will be instructed to contact the physician or nurse practitioner who will initiate therapy at 0.6 mg/day to avoid gastrointestinal symptoms. Subjects who do not tolerate an increased dose during escalation will have a delayed dose escalation by up to 7 days. Study medical staff also will help subjects develop a medication schedule, based on when and where subjects will take the medication each day and how they will remind themselves to do so.

Figure 2. Dosing Schedule for Liraglutide



After randomization, subjects will return at week 1 to assess rate of response. Subjects will return for study visits every two weeks thereafter, at weeks 3, 5, 7, 9, 11, 13, 15, and 17. Study staff will review the individual's medication adherence at each study visit, determining the number of days that liraglutide was used each week and identifying reasons for missed doses. The number of doses of medication taken each week will be tracked.

Medical assessment: Study visits include a brief medical visit (10-15 minutes) with a physician or nurse practitioner. These visits are needed for subjects to monitor their response to the medication. At each medical visit, subjects' weights and vital signs will be measured and their response to the medication will be assessed. Subjects will be asked whether there have been any changes in their health or medications. For all non-study-related medical events, subjects will be referred to their own PCPs.

Assessments for Efficacy

An assessment of binge frequency since the participant's last visit will be completed by the psychologist or Masters' level trained study staff by interview at each study visit based on the binge eating section of the EDE. Subjects also will be asked about their mood or any thoughts of harming themselves, as assessed by the Patient Health Questionnaire, 9 item version (PHQ-9) [31] and the Columbia-Suicide Severity Rating Scale (C-SSRS) [32]. In the event of reports of suicidal ideation or disturbances in mood, subjects will be referred to the study's psychologist or psychiatrist for further evaluation, as appropriate.

The Clinical Global Impression of Improvement scale (CGII) [24] will be used by the psychologist or master's level study staff to rate level of overall symptom improvement based on the information gathered at each treatment visit. This is a 7-point scale ranging from 1 – very much improved to 7 – very much worsened.

Additionally, participants will be assessed using several assessments at the randomization visit and each study visit for the secondary outcomes:

1. In addition to a safety assessment, the Patient Health Questionnaire 9-Item version (PHQ-9) [31] will be used to assess changes in mood during treatment.
2. The Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [43] is a face-valid survey of a broad range of quality of life items that we have used in several previous treatment trials for eating disorders.
3. The Yale-Brown Obsessive Compulsive Scale modified for BE (YBOCS-BE)[44] assesses the degree of obsessions that are focused on BE thoughts and compulsions that are focused on BE behaviors.
4. Weight will be measured at each visit, without shoes and in light clothing, on a calibrated Tanita scale measured to the nearest 0.1 kg.

In summary, study visits will consist of the vital sign and weight assessment, medical assessment with a physician or nurse practitioner, completion of written surveys (PHQ-9, QLES-Q, YBOCS-BE), review of the binge eating module of the EDE, C-SSRS, and CGII by study staff, and review of medication adverse events. All measurements and assessments will be recorded in the patient case report form. These visits are expected to last about 30-40 minutes. The study assessments at week 17 will consist of the full EDE, Eating Inventory, Loss of Control

Eating Scale, Yale Food Addiction Scale, FCQ-T, FCQ-S, NEQ, and PSQI in addition to the previously listed measures.

Assessments for Safety

Safety endpoints include physical examination, adverse events (AEs), standard laboratory tests, and mental health as assessed by the C-SSRS [32]. As detailed above, all subjects also will have brief medical visits (10-15 minutes) with a physician or nurse practitioner at weeks 0, 1, 3, 5, 7, 9, 11, 13, 15, and 17. These visits are to monitor subjects' response to the medication. Subjects will be asked whether there has been any change in their health or medications. They also will be asked about their mood (PHQ-9) or any thoughts of harming themselves, as determined by the C-SSRS. In the event of significant adverse mental health events, subjects will be referred to the study's psychologist or psychiatrist for further evaluation, if required. 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, lipids, hemoglobin A1c) at screening and week 17. Vital signs (blood pressure and pulse) and weight will be measured at screening and weeks 0, 1, 3, 5, 7, 9, 11, 13, 15, and 17.

As stated above, safety labs will be assessed at baseline and week 17. Fasting blood samples (i.e., following an 8 hour overnight fast) will be drawn on each of these occasions, including a complete blood count (CBC), comprehensive metabolic panel (CMP; including glucose), hemoglobin A1c (to identify pre-existing or the occurrence of diabetes mellitus), (for women) a urine pregnancy test, and assayed for triglycerides, total cholesterol, and LDL and HDL cholesterol. (Samples will be drawn and spun at our center, and shipped to be analyzed by Quest Diagnostics.) Each blood draw will require approximately 1 tablespoon (i.e., 15 mls) of blood. Blood pressure and pulse will be measured on each occasion using an automated monitor (Dinamap, model 9300). Two readings will be taken on each occasion (at 1-minute intervals), after participants have been seated for at least 5 minutes.

At baseline screening, participants will complete a history and physical examination and have an EKG. Interpretation of results will use the categories "normal", "abnormal", not clinically significant" or "abnormal, clinically significant". Subjects will be screened extensively (by a physician or nurse practitioner) to determine that they have no contraindications to the use of liraglutide or to possible weight loss.

Other Assessments

n/a

Subject Compliance

Subjects will be instructed to keep a medication diary to be reviewed at each visit, and they will be asked if they have missed any doses since their last visit. We will also measure 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 subjects if they are missing doses.

Assessing Adverse Events

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 participant's study endpoint. This includes adverse events that may be related to any study procedure (i.e., laboratory tests or ECGs) that may not have been performed during normal management of the participant, in addition to his/her use of liraglutide.

STATISTICAL CONSIDERATIONS:

Sample Size Calculation

A power analysis was conducted for the primary outcome, reduction in binge episodes per week (i.e., last 7 days). Estimated variances and clinically relevant treatment differences were derived from the literature using previous randomized controlled trials for BED [14, 45]. The common standard deviation used was 4.1 [45], and the clinically relevant change in binge episode used was 1.6 binge episodes per week [45]. Furthermore, a mixed effects model design assuming a compound symmetry covariance structure (congruent with the primary analytic plan) with a total of 10 assessment points and an ICC parameter equal to 0.59 (this is the value that was used as the auto correlation rho in PASS), estimated based on data collected from similar populations within our Center for Weight and Eating Disorders [46], i.e., reduction in nocturnal ingestions per week among patients with night eating syndrome with an SSRI. There is often overlap between persons with night eating syndrome and BED and we believe that the variance in improvements from week to week in core symptoms of these disorders would be similar. Based on these estimates, a baseline sample size of 152 participants (76 per group) with a 15% attrition rate (actual total n=132) will give 80% power to detect a clinically relevant mean difference in degree of reduction in binge episodes of 1.6 per week (effect size: 0.39) to be significant at alpha = 0.05, based on a two-sided test. All secondary outcomes will be considered exploratory and evaluated at the alpha=0.05 level. However, those exploratory analyses will provide valuable findings on changes in weight and other clinically meaningful changes in eating disordered attitudes and behaviors that have not been examined previously in relation to the use of liraglutide. The power analysis was conducted using the PASS software, Version 11 NCSS LLC, Kaysville, UT [47].

Statistical Methods

Preliminary and descriptive analyses. All data will first be assessed for missing and out-of-range values with basic statistical procedures such as univariate statistics (means, confidence intervals, standard deviations, ranges, frequencies, proportions, percentiles) and graphs such as histograms, box and whisker plots, scatter plots and Q-Q plots. All questions of data quality will be investigated and resolved before any statistical modelling, as complete and accurate data are essential for unbiased estimates and confidence intervals.

Baseline and demographic characteristics will be summarized overall for all subjects and by treatment group. Means and confidence intervals will be provided for continuous variables and frequencies and percentages for categorical variables. Graphical methods mentioned above will be used to examine distributions and identify potential influential points. The balance of baseline measures across the two treatment groups will be compared using appropriate 2-sample tests, including Wilcoxon rank-sum and t-tests for continuous variables, and Fisher's exact and Pearson Chi-square tests for categorical variables. Any baseline variables found to be associated with treatment condition will be added to the outcome analysis as a covariate.

Primary analysis. The primary outcome is the degree of reduction in binge episodes per week. It is count data that is likely to be skewed, so a shifted log transformation will be considered to stabilize the distribution to better meet the normality assumptions. To address the primary aim 1, a mixed effects model will be fit with Treatment Group (liraglutide 3.0 mg/d and placebo) as a between subjects factor and Time (Weeks 1 through 17) as a categorical within-subjects factor. Time is treated as a categorical factor so that we can use the group-time interactions with the time main effect to estimate and test intention-to-treat (ITT) treatment group differences at each time point, with the 17-week time point as our primary ITT test. In fitting a mixed effects model with maximum likelihood, a variance-covariance structure must be selected. We will begin by assuming a compound symmetry structure, but also consider criteria such as the Akaike's Information Criterion (AIC) for selecting the best form of the variance-covariance structure using Residual Maximum Likelihood (REML) (e.g., Compound Symmetry, Toeplitz, first-order autoregressive, and unstructured). Furthermore, we will include as baseline covariates those variables that have been established to be associated with the outcome based on prior literature, including sex and age. The results from the mixed model will be summarized by mean (SE) change from baseline for each treatment group at each time point.

Given the above definition of the ITT tests under the mixed effects model, the main interest in this study is the to the test of the primary hypotheses that participants randomized to liraglutide 3.0 mg/d (N=76) will show superior improvements from baseline to treatment end (week 17) in the number of binge episodes per week as compared to those on placebo (N=76). The primary hypothesis will be evaluated at the alpha = 0.05 level and all other contrasts and secondary/tertiary outcomes/hypotheses will be considered exploratory and those results will be interpreted with caution at alpha equal to 0.05 level. Analyses will be conducted using the statistical software package, SAS for Windows (SAS Institute, Inc., Cary, NC) [48].

As a sensitivity analysis, we will alternatively use a negative binomial distribution to model the rate of binge eating episodes per week (taking into account the trial duration for individual subjects) and will count r as a number of binge eating episodes. The binge eating episodes per week ratio will be compared between the liraglitude and placebo groups.

Of note, the analysis plan for the primary outcome variable will remain the same, but the final sample size will be 36 instead of 152.

Analyses for Aim 2. To assess differences among the two conditions in the percentage of participants who were in remission (2 binary outcomes), generalized estimating equation (GEE) models will be fit with the same between group, within group, and interaction terms as presented above, as well as, any relevant baseline covariates. A binomial distribution will be specified using a logit link function, and the unstructured covariance matrix will be considered to adjust for the within subject clustering of repeated measures data. From the GEE models, odds ratios and 95% confidence intervals will be computed to compare the treatment groups at each time point.

Of note, this analysis will also be completed as proposed with the reduced sample.

Analyses for Aim 3. The mixed effects model approach described for the primary analysis will also be utilized to compare changes in body weight, global BED symptom improvement, cognitive restraint of food intake, dietary disinhibition, perceived hunger, quality of life, and depressed mood between treatment groups. Changes in these outcomes will also be summarized by mean(SE) for each treatment group at each time point. If violations in the normality assumption are observed, log transformations, as well as alternative distributions such as Poisson and Negative binomial will be considered.

Of note, cognitive restraint, disinhibition, and hunger will only be available for completers, so it is unlikely that this model can be run for these variables. The other variables in this aim were administered at each visit and can be included in the proposed models.

Safety analysis. Given the modest sample size, we will not perform safety analysis. Instead, safety labs will be reviewed on an individual basis with participants to assure that they are within normal limits, and these will be available in summary for publications/presentations. The details for reporting SAEs to the IRB and procedures for taking action to safeguard participants are described in the safety monitoring plan.

Missing data and statistical models. Every effort will be made to obtain follow-up data on all participants randomized. Based on prior studies that we have conducted, the dropout rate by 17 weeks could be as high as 15%. Our maximum likelihood approach assumes that any missing outcome data are missing at random (i.e., missing data, including those due to drop-out, but not dependent on any previously observed outcomes or treatment assignment). With this approach, we will use all data that have been collected, without regard to whether data are missing for a participant at another visit, including drop-out, and without explicit imputation of missing data. We will conduct sensitivity analyses to examine the impact of missing data. Details regarding the sensitivity analyses will be pre-specified prior to unblinding. Furthermore, we will assess whether dropout status or level of compliance is associated with treatment condition as well as baseline demographic variables using appropriate 2-sample tests, including Wilcoxon rank-sum and t-tests for continuous variables, and Fisher's exact and Pearson Chi-square tests for categorical variables, and all findings will be reported.

Change in frequency of binge episodes per week also will be analyzed using a per protocol analysis that, for liraglutide-treated participants, includes only those who were able to tolerate and adhered to the full dose of liraglutide 3.0 mg.

Interim Analysis

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

Explorative Statistical Analysis for Pharmacogenetics and Biomarkers

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

5.20.19 Of note, due to unforeseen low response to advertising and the mis-allocation of medication by our Investigational Drug Service, our number or participants with usable data is low. We are unable to continue to staff and run the study at this point.

Of the 21 participants enrolled in the first year, 5 participants were non-completers who were not affected by the IDS mis-allocation, 1 was a completer and was not affected by the misallocation, 9 received only one box of the same type of medication before being switched to the opposite (e.g., liraglutide to placebo or vice versa) and were censored, 4 received two boxes of the same medication or placebo consecutively and were retained, and 2 received three boxes of the same medication or placebo consecutively and were retained. Thus, this first year yielded 1 completer and 11 censored or drop-out participants. In the current year we randomized 16 participants, but one was censored without usable data given she had concealed that she was taking metformin, leaving 15 participants with usable data. Of these, 1 was lost to follow-up, 4 have completed the trial, and 10 are currently still active in the trial. In sum, we will include 36 participants in the proposed analyses.

DATA HANDLING AND RECORD KEEPING:

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

- Protected health information (PHI) collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of research subjects to revoke their authorization for use of their PHI
- View of PHI will be limited to individuals at the University of Pennsylvania directly involved in the study. The company donating the study product will not have access to PHI.

All electronic PHI will be maintained by using an institutionally secured and managed network drive, institutionally secured and managed devices, and institutionally approved third-party computing environments. Should PHI need to be transferred, it will be done so through the use of a Penn-approved encrypted portable drive or a Penn-approved secure encrypted file transfer solution.

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

Where possible, data will be entered directly into our password protected database, REDCap. All data pertaining to the study will be saved on the Center for Weight and Eating Disorders' password-protected server. Paper copies of informed consent, questionnaires, interviews, lab results, and any correspondence will be kept in the case record in locked offices.

ETHICS:

The principal investigator (PI) will initiate and enroll subjects only after receiving IRB approval of the protocol and the informed consent documents. All recruiting materials used in the study

will have IRB approval. Progress reports regarding the study will be submitted to the IRB in accordance with institutional and regulatory guidelines.

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

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

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

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

STUDY SCHEDULE:

Table 3. Study Schedule (quarterly)

	2017		2018				2019				2020			
Study start, IRB approval	6/1													
Recruitment														
First subject screening visit		7/1												
Enrollment/randomization		4-5 subjects/month												
Last subject first visit											12/1			
Data collection		7/1											4/1	
Data analysis/manuscripts														
Final study reports														

STUDY DRUGS AND MATERIALS:

Study medication(s) / devices(s)

Subjects assigned to liraglutide (Saxenda) or placebo will need 119 doses (5 pens). Subjects will be provided with a 30-day supply of medication or placebo (1 pen) on 5 occasions (380 of each). We will assign 76 subjects to liraglutide and 76 subjects to placebo.
Of note, we will complete the study with 36 participants total.

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

Packaging and Labelling of Study Medication(s)

Novo Nordisk's Clinical Supplies (CS) will deliver study drugs (both Saxenda and placebo), as ready-to-use, pre-filled, multi-dose pens. Clinical Services will complete the labelling and packaging of the pens, and ship the labelled study drugs to the Investigational Drug Service (IDS) at the University of Pennsylvania (attention Dr. Ken Rockwell). The labels will have all information required by US Health Authorities.

CS will use a Dispensing Unit Number (DUN) on the label, which will be linked to the randomization scheme (created at IDS at Penn). "Instructions for Use" will not be inside the study drug box, but will be provided by CS as a print page that will be included in the first drug shipment to site.

Storage and Drug Accountability of Study Medication(s)

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

We will maintain adequate drug inventory and security at all times. Upon receipt of the study drug, the 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 study investigators will immediately notify Novo Nordisk (or its designee) or the drug distribution contractor of any damaged or unusable study drug that the center receives, and document in the inventory log any damaged or unusable study drug. We will request that additional study drug be shipped as needed.

The drug supplies will be kept in a secured enclosure with limited access, 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. 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. The investigator will return all unused drug to Novo Nordisk or its designee, unless alternative arrangements for drug disposal are authorized. No study drug will be retained when the study is completed; all study drugs will be returned to Novo Nordisk or its designee for destruction.

Auxiliary Supply

No auxiliary supplies are planned.

Randomization and Blinding

Dr. Ken Rockwell from Penn's Investigational Drug Service will generate the randomization code. The randomization will be generated using a 1:1 randomization scheme of liraglutide or placebo. The first subject to meet the treatment criteria will be assigned the first number in the sequence; each subsequent subject to meet treatment criteria will be assigned the next number in the sequence. This is a randomized, double-blind, placebo-controlled trial with a parallel groups design.

Breaking of Blinded Codes

Unblinding of the treatment codes will occur after all data have been verified and deemed clean by the data managers and statistician, and right before analysis of the data occurs.

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 staff-member breaking the code will record the time, date and reason as well as his/her initials in the source documents. All codes (whether broken or not) will be kept throughout the trial period. Accountability of all broken or unbroken codes (hard copy or electronic) will be performed at or after trial closure.

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.

ADERSE EVENTS:

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

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

Definitions

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 follow-up period, as defined in the protocol.

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

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

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

Serious Adverse Drug Reaction (SADR):
An adverse drug reaction (ADR) is an adverse event for which a causal relationship (Possible/Probable relation) between the study drug and the occurrence of the event is suspected. The ADR should be classified as **serious** if it meets one or more of the seriousness criteria.
SUSAR (Suspected Unexpected Serious Adverse Reaction)
An SAE which is unexpected and regarded as possibly or probably related to the trial/study product by the sponsor-investigator, Dr. Allison.

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

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

Severity Assessment Definitions:

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

Relationship to study medication Assessment Definitions:
• Probable: Good reasons and sufficient documentation to assume a causal relationship
• Possible: A causal relationship is conceivable and cannot be dismissed
• Unlikely: The event is most likely related to an etiology other than the trial product
The PI (Dr. Allison) will evaluate all unexpected events and adverse reactions.

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

Collection, Recording and Reporting of Adverse Events
All events meeting the definition of an adverse event will be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the post-treatment follow-up period as stated in the protocol.
At a minimum the following information will be reported:

- Study name
- Patient identification (e.g. subject number, initials, sex, age)
- Event (Preferably diagnosis)
- Trial drug
- Reporter
- Causality
- Outcome

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

Pregnancy
Study subjects will be instructed to notify the sponsor-investigator, Dr. Allison, immediately if they become pregnant, discontinue the study drug, and consult an obstetrician or maternal-fetal

medicine specialist. The study physician or nurse practitioner will confirm via self-report that the participant is consulting with an obstetrician or maternal-fetal medicine specialist, record all complications, and obtain information regarding the overall health of the mother and baby once per trimester and post-delivery. The investigator will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by the investigator will occur within the same timelines described above for reporting of Adverse Events. Pregnancy complications will be recorded as an adverse event(s). If the infant has a congenital anomaly/birth defect this will be reported and followed up as a serious adverse event.

Precautions/Over-dosage

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

LIABILITY AND SUBJECT INSURANCE:

During and following a subject's participation in trial, Dr. Allison and Penn Medicine 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 for study subjects will be provided regardless of their insurance status.

Dr. Allison will be responsible for the conduct of the study and agrees to defend, indemnify, and hold harmless Novo Nordisk, any of its parent companies, affiliates, or subsidiaries, and their respective officers, directors, employees, agents, representatives, distributors, salespersons, customers, licensees, and end-users from and against any claim, suit, demand, loss, damage, expense or liability imposed by any third party arising from or related to: (a) any breach of sponsor-investigator's obligations or representations; or (b) sponsor-investigator's negligent or grossly negligent use or willful misuse of the study drug, the results, or services derived therefrom. This indemnification shall not apply in the event and to the extent that a court of competent jurisdiction or a duly appointed arbiter determines that such losses or liability arose as a result of Novo Nordisk's gross negligence, intentional misconduct, or material breach of its responsibilities.

EVALUABILITY OF SUBJECTS:

Subjects 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. Any censorship will be documented in case records and appropriately reported.

PK and/or PD Modelling

No PK/PD modelling is planned in this trial.

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

Of note, we have stopped recruitment and will terminate the study after the last enrolled participants completes study visits (anticipated at the beginning of September, 2019). This was due to low yield from recruitment efforts as well as the misallocation of drug and placebo by IDS affected the number of participants with usable data.

PUBLICATION PLAN:

We will register the study with a publicly assessable database, e.g., clinicaltrials.gov. An initial report of the findings will be presented at an annual scientific meeting (e.g., The Obesity Society's Obesity Week and/or The Academy for Eating Disorders' International Conference on Eating Disorders). We plan to publish the study results approximately 6 months after study completion.

The report of the primary outcome will be submitted to International Journal of Eating Disorders. If not accepted, we would submit it next to the Journal of Eating and Weight Disorders. A secondary paper likely will be submitted regarding the clinical significance of the size of binge eating as compared to the degree of loss of control in relation to the current diagnostic criteria for BED to the International Journal of Eating Disorders or Frontiers in Eating Behavior.

REFERENCES:

1. Stunkard AJ. Eating patterns and obesity. Psychiatr Q. 1959; 33:284-94.
2. Spitzer RL, Yanovski S, Wadden T, Wing R, Marcus MD, Stunkard A, Devlin M, Mitchell J, Hasin D, Horne RL. Binge eating disorder: its further validation in a multisite study. Int J Eat Disord. 1993;13:137-53.
3. Javaras KN, Pope HG, Lalonde JK et al. Co-occurrence of binge eating disorder with psychiatric and medical disorders. J Clin Psychiatry 2008;69:266-73.
4. Grilo, C. M., White, M. A., Masheb, R. M. DSM-IV psychiatric disorder comorbidity and its correlates in binge eating disorder. Int J Eat Disord. 2009;42:228-234.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. American Psychiatric Association, 2013.
6. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007;61:348.
7. Hay P, Girosi F, Mond J. Prevalence and sociodemographic correlates of DSM-5 eating disorders in the Australian population. J Eat Disord. 2015;3:19. doi: 10.1186/s40337-015-0056-0. eCollection 2015.
8. Allison KC, Stunkard AJ. Obesity and eating disorders. Psychiatr Clin North Am. 2005; 28(1):55-67.
9. Allison KC, Wadden TA, Sarwer DB, Fabricatore AN, Crerand CE, Gibbons LM, Stack RM, Stunkard AJ, Williams NN. Night eating syndrome and binge eating disorder among persons seeking bariatric surgery: prevalence and related features. Obesity. 2006;14 Suppl 2:77S-82S.
10. Kessler RC, Berglund PA, Chiu WT, Deitz AC, Hudson JI, Shahly V. et al. The Prevalence and Correlates of Binge Eating Disorder in the World Health Organization World Mental Health Surveys. Biological Psychiatry 2013; 73:904-914.

11. Winkler LA, Christiansen E, Lichtenstein MB, Hansen NB, Bilenberg N, Støving RK.Quality of life in eating disorders: a meta-analysis. Psychiatry Res. 2014 Sep 30;219(1):1-9.
12. Stunkard AJ, Allison KC. Binge eating disorder: disorder or marker? Int J Eat Disord. 2003;34 Suppl:S107-16.
13. Allison KC, Grilo CM, Masheb RM, Stunkard AJ. Binge eating disorder and night eating syndrome: A comparative study of disordered eating. J Consult Clin Psychol. 2005;73(6):1107-1115.
14. McElroy S, Mitchell J, Wilfley D et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. JAMA Psychiatry, in press, doi:10.1001/jamapsychiatry.2014.21624.
15. McElroy SL, Hudson JI, Malotra S, Welge JA, Nelson EB, Keck PE. Citalopram in the treatment of binge eating disorder: a placebo-controlled trial. J Clin Psychiatry 2003;64:807-813.
16. McElroy SL, Guerdjikova AI, Mori N, O'Melia AM. Pharmacological management of binge eating disorder: current and emerging treatment options. Therapeutics and Clinical Risk Management 2012; 8:219-214.
17. Leombruni P, Lavagnino L, Fassino S. Treatment of obese patients with binge eating disorder using topiramate: a review. Neuropsychiatr Dis Treat. 2009;5:385-92.
18. Wilfley DE, Crow SJ, Hudson JI, Mitchell JE, Berkowitz RI, Blakesley V, Walsh BT; Sibutramine Binge Eating Disorder Research Group. Efficacy of sibutramine for the treatment of binge eating disorder: a randomized multicenter placebo-controlled double-blind study. Am J Psychiatry. 2008 Jan;165(1):51-8.
19. AHRQ Evidence-based Practice Center Program. Management and Outcomes of Binge-Eating Disorder (BED). EHC-2014-08-0050.R1. To be released in Fall, 2015.
20. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, Aronne L; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes. 2013;37(11):1443-51.
21. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373(1):11-22.
22. Robert SA, et al. Improvement in binge eating in non-diabetic obese individuals after 3 months of treatment with liraglutide — A pilot study. Obes Res Clin Pract. 2016;9(3):301-4.
23. Gormally J, Glack S, Daston S, Rardin D. The assessment of binge eating severity among obese persons. Addict Behav. 1982;7:47–55.
24. Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: Psychopharmacology Research Branch, National Institute of Mental Health; 1976.
25. Stunkard A, Berkowitz R, Tanrikut C, Reiss E, Young L. d-fenfluramine treatment of binge eating disorder. Am J Psychiatry. 1996;153(11):1455-9.
26. Reas DL, Grilo CM. Pharmacological treatment of binge eating disorder: update review and synthesis. Expert Opin Pharmacother. 2015;16(10):1463-78.
27. Jacobs-Pilipski MJ, Wilfley DE, Crow SJ, Walsh BT, Lilenfeld LR, West DS, Berkowitz RI, Hudson JI, Fairburn CG. Placebo response in binge eating disorder. Int J Eat Disord. 2007;40(3):204-11.

28. Corwin RL, Boan J, Peters KF, Ulbrecht JS. Baclofen reduces binge eating in a double-blind, placebo-controlled, crossover study. Behav Pharmacol. 2012 Sep;23(5-6):616-25.
29. Guerdjikova AI, McElroy SL, Winstanley EL, Nelson EB, Mori N, McCoy J, Keck PE Jr, Hudson JI. Duloxetine in the treatment of binge eating disorder with depressive disorders: a placebo-controlled trial. Int J Eat Disord. 2012 Mar;45(2):281-9.
30. Guerdjikova AI, McElroy SL, Welge JA, Nelson E, Keck PE, Hudson JI. Lamotrigine in the treatment of binge-eating disorder with obesity: a randomized, placebo-controlled monotherapy trial. Int Clin Psychopharmacol. 2009 May;24(3):150-8.
31. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–13.
32. Posner K, Brent D, Lucas C, et al. Columbia-Suicide Severity Rating Scale (C-SSRS). New York, NY: Columbia University Medical Center; 2008
33. EDE Fairburn CG, Cooper Z, O'Connor ME. The Eating Disorder Examination. 16th Ed. In C.G. Fairburn. Cognitive Behavior Therapy and Eating Disorders. New York: Guilford, 2008;265-308.
34. Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G. The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview. J Clin Psychiatry. 1998;59(20):22-33.
35. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res. 1985;29:71-83.
36. Latner JD, Mond JM, Kelly MC, Haynes SN, Hay PJ. The loss of control over eating scale: development and psychometric evaluation. Int J of Eat Disord. 2014; 47(6):647-659.
37. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. Appetite. 2009; 52:430-436.
38. Bagby MR, Parker JDA, Taylor GJ. The twenty-item Toronto Alexithymia Scale-I. Item selection and cross-validation of the factor structure. J of Psychometric Research. 1994; 38(1):23-32.
39. Allison, KC, Lundgren JD, O'Reardon JP, Martino NS, Sarwer DB, Wadden TA, Crosby RD, Engel SG, Stunkard AJ. The Night Eating Questionnaire (NEQ): Psychometric properties of a measure of severity of the Night Eating Syndrome. Eat Behav. 2008;9:62-72.
40. Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Res. 1988;28:193-213.
41. Cepeda-Benito A, Gleaves DH, Williams TL, Erath SA. The development and validation of the state and trait food-cravings questionnaires. Behav Ther. 2000;31(1):151-173.
42. Liraglutide (rDNA origin) injection [package insert]. Plainsboro, NJ: Novo Nordisk, Inc.; 2014.
43. Endicott J, Nee J, Harrison W et al. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q): A new measure. Psychopharmacological Bulletin, 1993; 29: 321-6.
44. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. Arch Gen Psychiatry. 1989;46(11):1006-11.
45. McElroy SL, Hudson JI, Capece JA, Beyers K, Fisher AC, Rosenthal NR; Topiramate Binge Eating Disorder Research Group. Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. Biol Psychiatry. 2007;61(9):1039-1048.

46. Allison KC, Studt SK, Berkowitz RI, Hesson LA, Moore RH, Dubroff JG, Newberg A, Stunkard AJ. An open-label efficacy trial of escitalopram for night eating syndrome. Eat Behav. 2013;14:199-203.
47. Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.
48. SAS Institute Inc. 2011. SAS® Component Language 9.3: Reference. Cary, NC: SAS Institute Inc.