Protocol Title

A Randomized, Placebo-Controlled Study of Liraglutide 3mg daily (Saxenda®) in Obese or Overweight Patients with Stable Bipolar Disorder

INVESTIGATOR-INITIATED STUDY PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN)

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BACKGROUND AND SIGNIFICANCE:

Obesity is common among persons with severe mental illness (SMI), especially those with bipolar disorder (BP) (1-5). It is estimated that 45-55% of people with SMI are obese, making obesity 1.5-2 times more common among those with SMI than among the general population (6). Indeed, in a recent pragmatic lithium trial conducted in BP, 69% of the subjects were overweight or obese (7). Although the precise mechanism underlying the relationship between obesity and SMI is unknown, it is thought to be multifactorial, involving genetic factors, intrinsic features of SMI (e.g., overeating, poor dietary choices, sedentary lifestyle, and sleep dysregulation), and the weight-gaining effects of most of the psychotropic medication used to treat SMI (1-4, 6, 8-10)

Importantly, obesity is thought to contribute to the well-documented elevated mortality from cardiovascular disease (CVD) among those with BP (11-15). Thus, weight reduction in obese people with BP might be important for reducing their morbidity and mortality from CVD and other obesity-related conditions (e.g., diabetes and metabolic syndrome). Conversely, the presence of obesity in patients with BP is associated with a more severe course of illness (16, 17), a lower health-related quality of life (18), reductions in brain gray and white volumes (19, 20), and non-adherence with antipsychotic medications (21). Indeed, it has been hypothesized that successful treatment of obesity in those with BP might benefit mental as well as physical health (17). It is thus imperative that obesity be a focus of treatment in those with BP.

Comprehensive behavioral weight management programs have shown some effectiveness for obesity in patients with SMI, but the weight loss is modest at best and such programs are difficult to implement and not widely available (22-25). Several medications have been shown to mitigate psychotropic-induced weight gain, particularly metformin and topiramate, but many patients either do not respond to these agents or are unable to tolerate them (2). Importantly, the efficacy and safety of newly available weight-loss agents have not been evaluated in people with SMI.

In December 2014, the U.S. Food and Drug Administration approved liraglutide [rDNA origin] 3 mg/day subcutaneous [sc] injection) (Saxenda®) as a treatment option for chronic weight management in individuals with obesity (26-32). The drug is approved for use in adults with a body mass index (BMI) of 30 or greater (obesity) or adults with a BMI of 27 or greater (overweight) who have at least one weight-related comorbid condition such as hypertension, type 2 diabetes, or dyslipidemia (33). Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Saxenda® and Victoza® contain the same active ingredient (liraglutide) at different doses (3 mg and 1.8 mg, respectively). However, unlike Victoza®, Saxenda® is not indicated for the treatment of type 2 diabetes, as the safety and efficacy of Saxenda® for the treatment of diabetes has not been established.

Several lines of evidence suggest that liraglutide 3.0 mg sc injection (Saxenda®), in combination with a reduced-calorie diet and increased physical activity, would be a useful weight-loss treatment for patients with BP who are overweight or obese.

First, GLP-1 is a gut/brain peptide that is secreted from intestinal mucosal enteroendocrine L cells in response and in proportion to nutrient stimulation of the gut, and that suppresses food intake by acting on receptors in key areas of the brain that regulate energy balance (e.g., hypothalamus and hindbrain) (34-37). In humans, administration of GLP-1 reduces food intake and increases satiation in a dose-dependent manner (37). Obesity in people with BP, as well as psychotropic-induced weight gain, are thought to be

due to in part to increased food intake (2). It is thus possible that liraglutide 3.0 mg sc injection will decrease food intake in obese patients with BP, thereby reducing body weight.

Second, preliminary preclinical and clinical findings suggest liraglutide 3.0 mg sc injection may be effective for antipsychotic-induced weight gain and antipsychotic-induced obesity (38). Thus, liraglutide has been shown to produce weight loss in animal models of olanzapine-induced weight gain (39, 40). In one of these studies, liraglutide also produced antidepressant-like effects (40). (Indeed, other animal studies suggest that liraglutide may have antipsychotic properties (41).) In the only published case of liraglutide use in a patient with SMI, an obese (BMI 33.5=mg/kg^2) 60-year-old woman with schizophrenia treated with clozapine, liraglutide (1.8mg/day) produced a sustained weight loss of 7.7 kg (an 8.7% body weight reduction) over two years (42). Liraglutide was well tolerated and there were no psychiatric adverse events (i.e., the patient's schizophrenia remained stable). At our own center, we have treated a 32-year-old woman with schizoaffective disorder, bipolar type and obesity (BMI=36 mg/kg^2) receiving one depot and two oral antipsychotics with liraglutide 3.0 mg sc injection and, to date, she has lost 7.5 kg (an 8.3% body weight reduction) over a 4-month period. She reports the liraglutide 3.0 mg sc injection has reduced her hunger and improved her satiety. She has tolerated liraglutide 3.0 mg sc injection well and has had no difficulties with giving herself the injections, her psychological symptoms have remained stable, and there have been no adverse psychiatric effects. Indeed, her mild tardive dyskinesia is much improved

Third, relative to other weight loss agents, liraglutide 3.0 mg sc injection has a favorable psychiatric and cardiovascular adverse event profile (43, 44). Regarding psychiatric events, in the pivotal liraglutide 3.0 mg sc injection clinical trials, 6 (0.2%) of 3384 liraglutide 3.0 mg sc injection-treated patients had suicidal ideation (one of these individuals made a suicide attempt) compared with none of the 1941 placebo-treated patients (33). Additionally, 2.4% of liraglutide 3.0 mg sc injection recipients had insomnia and 2.0% had anxiety, compared with 1.7% and 1.6 %, respectively, of placebo recipients. Conversely, lorcaserin (Belviq®) was associated with euphoria (0.2% vs < 0.1% for placebo) and is contraindicated in patient's receiving serotonergic medications (and many psychotropics enhance serotonin function) (45). Phenermine/topiramate combination (Qsymia®), at the highest approved dose, was associated with insomnia (11.1% vs 5.8% for placebo), depression/mood problems (7.6% vs 3.4% for placebo), and anxiety (7.9% vs 2.6% for placebo) (46). Additionally, one of the components of Qsymia®, topiramate, is associated with suicidality. Bupropion/naltrexone combination (Contrave®), at the highest recommended dose, was associated insomnia (9.2% vs 5.9% for placebo), anxiety (4.2% vs 2.8% for placebo), and irritability (2.6% vs 1.8% for placebo) (47). Moreover, there are reports of components of these latter medications (e.g., phentermine and bupropion) causing severe adverse psychiatric events, such as mania and psychosis (48-52). Taken together, these findings suggest that liraglutide 3.0 mg sc injection may be the least likely of these weight management medications to exacerbate psychiatric symptoms in people with BP. Indeed, GLP-1 analogues have been reported to produce enhanced well-being in patients with diabetes (53).

Taken together these data support the hypothesis that liraglutide 3.0 mg sc injection will reduce body weight and improve metabolic variables in obese or overweight patients with BP without worsening psychiatric symptoms. We predict that liraglutide 3.0 mg sc injection will display greater efficacy as compared to placebo in decreasing body weight in patients with BP who are obese or overweight. To prove this hypothesis, we will conduct a single-center, randomized, placebo-controlled, double-blind, parallel-group, 2-arm clinical trial of liraglutide 3.0 mg sc injection in 60 obese or overweight outpatients

with stable BP. We have chosen BP rather than another SMI because it is the most common SMI (more common than schizophrenia or schizoaffective disorder) and has a particularly strong association with obesity.

SPECIFIC OBJECTIVES:

Primary Objective:

The primary objective of this study is to evaluate the efficacy of liraglutide 3.0 mg sc injection (in combination with a reduced calorie diet and increased physical activity) compared with placebo for reducing body weight in obese or overweight adults with stable BP, as measured by percent change in body weight.

Secondary Objectives:

Secondary objectives are:

- To evaluate the efficacy of liraglutide 3.0 mg sc injection as measured by:
  - Proportion of participants who have a ≥ 5% loss in body weight
  - Body weight (kg)
  - BMI
  - Waist circumference
  - Fasting lipids
  - Fasting glucose
  - $HgA1_c$ levels
  - Three-Factor Eating Questionnaire (TFEQ) (54)
  - Binge Eating Scale (BES) (55)
- To evaluate the safety and tolerability of liraglutide 3.0 mg sc injection, using:
  - Mental status examinations
  - Young Mania Rating Scale (YMRS) (56)
  - Montgomery Asberg Depression Rating Scale (MADRS) (57)
  - Clinical Global Impressive Scale for modified Bipolar Disorder (CGI-BP) (58)
  - Physical examinations
  - Vital signs
  - 12-lead electrocardiograms (ECG)
  - Clinical laboratory tests
  - Adverse event reports
  - Columbia-Suicide Severity Rating Scale (C-SSRS) (59)

RESEARCH DESIGN AND METHODS

Study hypothesis (es):

The central research question is whether liraglutide 3.0 mg sc injection is efficacious for reducing body weight in obese or overweight patients with BP. We hypothesize that liraglutide 3.0 mg sc injection will be an efficacious, safe, and well tolerated treatment for weight loss in obese or overweight patients with stable BP. We predict that liraglutide 3.0 mg sc injection will display greater efficacy as compared to placebo in decreasing body weight in patients with BP who are overweight or obese without increasing psychiatric adverse events. We also predict that liraglutide 3.0 mg sc injection will produce a greater

percentage of patients who lose ≥ 5% of baseline body weight, and improve BMI, waist circumference, fasting lipid and glucose levels, $HgA1_c$ levels, and measures of eating psychopathology.

Endpoints:

The primary endpoint will be the percent change in body weight from Baseline (Week 0) to week 40/Early Termination (ET) (see Table 1 for a schedule of assessments). Secondary endpoints will include proportion of participants who lose ≥ 5% of baseline body weight, and change from baseline in body weight (kg), BMI, waist circumference, and metabolic variables (fasting lipids and glucose, and $HgA1_c$ levels). Exploratory secondary endpoints will be change from baseline in eating psychopathology, assessed with the Three Factor Eating Questionnaire (TFEQ) (54) and Binge Eating Scale (BES) (55). Safety endpoints assessed at each study visit will be mental status examination, clinically-administered scales that assess psychopathology (CGI-BP scale [both Severity and Improvement subscales], YMRS, MADRS, and CSSRS), vital signs, and adverse events determined by clinical interview. Laboratory tests and 12-lead electrocardiograms (ECGs) will be obtained at Screening, week 8, week 16/ET, and week 40/ET. Compliance will be assessed at each visit with inspection of returned multi-dose pens. Potential interactions between liraglutide and psychiatric medications will be monitored and recorded on the Potential Drug Interaction form (see p. 28).

Study type:

This is a single-center, randomized, placebo-controlled, double-blind, two-arm, parallel-group, fixed-dose efficacy and safety study with 3 phases: a 3-27 day Screening period; a 40-week randomized, double-blind Treatment period (4 weeks of dose titration and 36 weeks of dose maintenance); and a 1-week Follow-up (drug discontinuation) period. The purpose of the 40-week Blinded Treatment phase is to establish the efficacy of liraglutide 3.0 mg sc injection for weight loss in obese patients with stable BP.

Study population:

We expect to screen about 90 subjects in order to randomize 60 subjects in a 1:1 ratio to drug or placebo. Patients will be recruited from the Lindner Center of HOPE, Mason, OH, a University of Cincinnati College of Medicine Affiliate. Patients will be recruited by clinician referral and advertisement.

Participants will include 60 outpatients with a DSM-IV (60) diagnosis of BP that is stable, who are obese or overweight with at least one weight-related comorbidity, and who have been receiving a stable psychotropic regimen for the past three months. The weight-related comorbidities to be included will be hypertension, type 2 diabetes, and dyslipidemia. Allowed psychotropic medications for BP will include mood stabilizers (lithium, valproate, and lamotrigine), antipsychotics (asenapine, aripiprazole, cariprazine, chlorpromazine, clozapine, haloperidol, loxapine, olanzapine, paliperidone, perphenazine, quetiapine, resperidone, thiothixene, trifluoperazine, or ziprasidone), antidepressants, and anxiolytics (benzodiazepines, gabapentin or pregabalin, and buspirone). Stable BP will be operationally defined as a CGI-BP-Severity score of 1through 3 (1= normal, not at all; 2= borderline mentally ill; 3=mildly ill); a YMRS score ≤12; a MADRS score ≤19, and the absence of clinically significant suicidality and psychosis. Participants must be 18 through 65 years of age, be able to provide informed consent, and if female, be postmenopausal, surgically incapable of childbearing, or practicing a medically acceptable method(s) of contraception (e.g., hormonal method, intrauterine device) for at least 1 month prior to study entry and throughout the study. Exclusion criteria include subjects with a lifetime DSM-IV Axis I diagnosis of dementia, a psychotic or depressive disorder, or a sub

stance use disorder within the past three months; those with clinically significant psychotic features or suicidal ideation; those with serious or unstable general medical illnesses; those with a personal or family history of medullary thyroid cancer or Multiple Endocrine Neoplasia syndrome type 2; those who are allergic to or who have demonstrated hypersensitivity to liraglutide 3.0 mg sc injection or any of its components; and females who are pregnant, nursing, or intend to become pregnant. Specific entry criteria are listed below.

Inclusion Criteria: Criteria for entering this study will include all of the following:

1. Men and women, ages of 18-65 years, inclusive.
2. Participants will have a DSM-IV bipolar disorder that is clinically stable.
3. Participants will have received a stable major psychotropic drug regimen (except for minor dosage adjustments) for at least 3 months prior study entry. Major psychotropic drugs are antipsychotics, mood stabilizers, and antidepressants. Subjects may have had changes in adjunctive benzodiazepines and hypnotic agents.
4. Participants will be obese (defined as a BMI $\geq$ 30 mg/kg^2) or overweight (defined as BMI $\geq$ 27 kg/m^2) with at least one weight-related comorbidity, such as hypertension, type 2 diabetes, or dyslipidemia.
5. Participants in treatment for a weight-related comorbidity (hypertension, type 2 diabetes, and/or dyslipidemia) must be on a stable and allowed treatment regimen for that condition for at least 3 months prior to study enrollment.
6. Participants will be able to provide informed consent before any trial-related activities.

Exclusion Criteria: Criteria for exclusion from this study will include any of the following:

1. Women who are pregnant, lactating, or of childbearing potential who are not using adequate contraceptive measures. The following are considered to be adequate methods of birth control: 1. Intrauterine device (IUD); 2. Barrier protection; 3. Contraceptive implantation system (Norplant); 4. Oral contraceptive pills; 5. A surgically sterile partner; and 6. Abstinence. Women who are > 2 years post-menopausal or surgically-sterile are not considered of childbearing potential. All female participants will have a negative pregnancy test prior to randomization.
2. Participants who have made a suicide attempt in the last 10 years, who are displaying clinically significant psychotic features, suicidality, or homicidality on mental status examination, or who have suicidal ideation or behavior as assessed with the C-SSRS**.**
3. Participants who are receiving behavioral weight loss treatment (BWLT) (e.g., Weight Watchers) that was begun within the 3 months before study entry. Participants who are receiving BWLT that was started 3 months prior to the beginning of the study will be allowed to continue to receive their BWLT during the trial only if they have had no weight loss in the past 3 months and they agree to not make any changes in the frequency or nature of their BWLT during the course of the drug trial.
4. A DSM-IV diagnosis of a substance-related or addictive disorder (except a tobacco-related disorder) within the 3 months prior to enrollment.
5. A **DSM-**IV diagnosis of dementia, a psychotic disorder, or a depressive disorder.
6. History of any psychiatric disorder which might interfere with a diagnostic assessment, treatment, or compliance.
7. Clinically unstable medical disease, including cardiovascular, hepatic, renal, gastrointestinal, pulmonary, neurological, metabolic, endocrine, or other systemic disease. Clinically stable hypertension, type 2 diabetes, or dyslipidemia are not exclusionary.

8. Have a history of a structural cardiac abnormality, valvular cardiac disease, cardiomyopathy, serious heart rhythm abnormality, coronary artery disease, congestive heart failure, stroke, or other serious cardiovascular problem.
9. Have an ECG with significant arrhythmias or conduction abnormalities, which in the opinion of the physician investigator preclude study participation.
10. Have clinically relevant abnormal laboratory results.
11. Participants requiring treatment with any drug which might interact adversely with or obscure the action of the study medication. This includes anti-obesity drugs, psychostimulants, modafinil or armodafinil, and topiramate or zonisamide. Participants receiving metformin at a stable dose for ≥ 3 months can be included.
12. Participants receiving GLP-1 based therapies, sodium-glucose co-transporter 2 inhibitors (SGLT2s), thiazolidinediones, sulfonylureas, or insulin.
13. Participants with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2.
14. Participants who have received any investigational medication within three months prior to randomization.
15. Participants previously screen-failed or randomised to participate in this trial.
16. Participants who have a known or suspected allergy to liraglutide 3.0 mg sc injection, its constituents, or related products.
17. Participants with a urine drug screen positive for a drug that, in the opinion of the investigator, is being abused.
18. Participants with a past medical history of pancreatitis.
19. Participants who had received any investigational drug within 3 months prior to this trial.
20. Participants who require bariatric surgery or are anticipated to require it during the course of the trial. If such surgery becomes warranted during the study, such patients will be excluded from the primary endpoint analysis.

Withdrawal Criteria:

Participants may withdraw at will from the study at any time. Participants will be withdrawn in the event of pregnancy or intention to become pregnant. Additionally, participants will be discontinued if they display: clinically significant suicidality, defined as a YES to item 1 of the C-SSRS or a C-SSRS-defined suicide attempt; a YMRS score >12 (indicating at least moderately ill manic symptoms); a MADRS score >19 (indicating at least moderately severe depressive symptoms); a CGI-I-BP-Severity score of much or very much worsened; or clinically significant suicidal ideation or psychotic symptoms on mental status examination. In the absence of the above, participants will be terminated at the treating psychiatrist's discretion in response to symptoms of sufficient severity that a new psychiatric medication needs to be added (dosage changes in ongoing psychotropics will be permitted). The Investigator may also withdraw participants for lack of compliance with study procedures if she or the research team has any concerns for the participant's safety. Upon termination for any of these reasons, patients will receive care judged appropriate by the treating investigators including, if needed, referral for emergency care.

Participant compliance with dosing requirements will be monitored with pen inspection. Participants displaying non-compliant behaviors with study medication administration and accountability (such as

taking more medication than prescribed, losing pens, or failure to return pens to clinic) will be re-educated. .

Subject Replacement:
Subjects will not be replaced if they withdraw or become ineligible at any time after the Baseline visit.

Rational for study population:
Approximately half of persons with BP are obese, yet no medication is regularly used (or indicated) for weight loss in this population, signifying a large unmet medical need. Data showing that a weight loss drug is beneficial in obese persons with BP would be a significant advancement to the medical field.

Visit Procedures:
During Screening, patients will be evaluated for eligibility. During the 40-week Blinded Treatment period, patients will be scheduled for weekly visits for the first 4 weeks of treatment (dose titration, Visit 0 through Visit 4), every other week for 12 weeks (dose maintenance, Visits 5 through 10), and then every 4 weeks for 24 weeks (continued dose maintenance, Visits 11-16) for assessments and study medication dispensation. After randomization to liraglutide 3.0 mg sc injection or placebo, patients will be permitted to have dosage changes in their major psychotropic medications (antipsychotics, mood stabilizers, and antidepressants), and such changes will be recorded on the concomitant medication form. Addition of these psychotropic medications will also be permitted and these medications will be recorded on the concomitant medication form.

All participants will be offered nutritional and lifestyle modification counseling following the 2015-2020 Dietary Guidelines for Americans (http://health.gov/dietaryguidelines/2015/guidelines/?linkId=20169028) at Baseline (Visit 0), Visit 4, Visit 6, Visit 8, and Visits 10-15.

Study medication will be supplied in pre-filled, multi-dose pens that can deliver the following doses subcutaneously: 0.6mg, 1.2mg, 1.8mg, 2.4mg, and 3mg. At the beginning of the Blinded Treatment period, the dosage of liraglutide will be 0.6 mg/day. Study drug dosage will be increased to 1.2mg/day on day 7 (Visit 1). In the following 3 weeks, the dose will be increased to 1.8mg/day (day 14, Visit 2), 2.4mg/day (day 21, Visit 3), and then to the target dose of 3mg/day (day 28, Visit 4), respectively. If patients do not tolerate an increased dose during dose escalation, the dose escalation can be delayed for approximately one additional week. The study medication dose (3 mg/day) will remain unchanged during the final 36 weeks of the Blinded Treatment Phase.

Study drug will be discontinued upon completion of the 40-week Blinded Treatment period (Visit 16) or if the subject terminates the study earlier (early termination, ET). The follow-up period begins upon completion of Visit 16 (week 40), ET (depending upon when the subject completes their study participation), and concludes with a follow-up visit (Visit 17) which occurs 7 days after Visit 16, or ET. Follow-up assessments include adverse events, concomitant medication form, potential drug interaction form, and termination record.

Listed below are the specific procedures to be done at each study visit.

Pretreatment Period Screening Visit (s):

The Screening period will be a minimum of 3 days and maximum of 28 days and be used to evaluate study candidates for inclusion and allow for wash-out of disallowed medications. At the first Screening visit (Visit -1), informed consent will be obtained. Sections A, B, and C of the Structured Clinical Interview for DSM-IV (SCID) (61) will be performed to establish that the patient meets DSM-IV criteria for BP. A mental status examination, YMRS, MADRS, and CGI-BP-Severity Scale will be performed to establish the severity of psychiatric symptoms. Medical history will be reviewed, a physical exam performed, and laboratory studies (complete metabolic profile with fasting glucose and lipids, CBC with diff and platelets, liver function tests, renal function tests, electrolytes, HgA_{1c} level, and urinalysis) and ECG will be obtained. Patients' mental health providers will be consulted about their suitability for study participation. Based on these evaluations, it will be determined whether participants meet entry criteria; participants meeting these criteria will continue in the screening process. The patient will not receive any disallowed medications during this period.

Patient screening requires:

1. Informed consent
2. Psychiatric evaluation and the Structured Clinical Interview for DSM-IV (61) to confirm the diagnosis of BP by DSM-IV criteria and evaluate protocol-specified subject selection requirements
3. Mental status examination
4. Medical History and physical eexamination (including vital signs, height, weight, and BMI determination)
5. Fasting blood draw for laboratory tests including serum β-HCG, CBC, TSH, liver and renal panels, electrolytes, lipid profile, glucose, and HgA_{1C} level. Of note, we have approved language from the University of Cincinnati IRB for use during the initial phone screen that allows us to instruct subjects to fast before they come to the Screening visit and sign informed consent. The phone screen form with the IRB-approved language is now listed on page 21(lines 908-915).
6. 12-lead Electrocardiogram (ECG)
7. Urinalysis and urine drug screen
8. YMRS
9. MADRS
10. CGI-BP-Severity Scale
11. C-SSRS lifetime version
12. Concomitant medication form
13. Adverse event form
14. Drug interaction form

Baseline Visit (Visit 0):

At Baseline, **s**ubjects meeting all of the inclusion/exclusion requirements will be randomized to drug or placebo in a 1:1 ratio. The baseline evaluation will consist of:

1. Inclusion/Exclusion Criteria checklist
2. Mental status examination
3. Vital signs, weight, waist circumference, and determine BMI
4. YMRS
5. MADRS
6. CGI-BP-Severity and -Improvement Scales

7. C-SSRS-since last visit
8. Urine pregnancy test
9. Three Factor Eating Inventory (TFEQ) (55)
10. Binge Eating Scale (BES) (54)
11. Concomitant medication form
12. Adverse events form
13. Potential drug interaction form
14. Counseling for reducing diet and increasing physical activity

Upon determination of continued eligibility, a subject identification number will be assigned and a prefilled dial-a-dose injection pen containing liraglutide or matching placebo will be dispensed along with instructions for its use. The first injection of study medication will be done at the end of the visit with guidance from the research team. The same rater will evaluate the subject throughout the study.

Blinded Treatment Period: Baseline Visit (Visit 0) Through Week 16 (Visit 40) or Early Termination (ET):

During the 40-week Blinded Treatment period, patients will be scheduled for weekly visits for the first 4 weeks of treatment (dose titration; Visits 0 through Visit 4), every other week for the next 12 weeks (dose-maintenance; Visits 5 through 10), and then every 4 weeks for the next 24 weeks (continued dose maintenance; Visits 11 through 16) for assessments and dispensation of study medication. At each visit from Baseline (Visit 0) through Visit 16, the participant will be evaluated for weight, vital signs, mental status examination, psychiatric symptoms, concomitant medications, adverse events, and potential drug interactions.

During the Treatment period, items 2-7, 8 and 11-14 from the Baseline evaluation will be repeated at each scheduled visit and at ET visits (see Table 1). In addition, items 9 and 10 will be repeated at Visits 4, 6, 8, and 10-16/ET. Laboratory tests, ECG, and urinalysis will be repeated at Visits 6, 10, and 16. Urine pregnancy tests will be performed at every visit (Visits 0-16/ET). Used and unused study medication and packaging will be collected and drug accountability assessed at every visit. Every effort will be made to keep the participant on the original time-frame for scheduled visits. If the participant deviates from this schedule, every effort will be made to return him/her to the original schedule of visits.

Participants will be instructed to bring their used and unused study medication and packaging to every visit. Participant compliance and drug accountability will be assessed by the investigator at every treatment phase visit by individual pen inspection and entered on the drug accountability log. Participants taking 80-100% of prescribed study medication will be considered compliant.

Final Treatment Phase Evaluation (Week 40 or ET):

Study drug will be discontinued upon completion of the Blinded Treatment phase (Week 40; Visit 16) or if the participant terminates the study earlier (early termination, ET).

The following evaluations will be conducted at the final treatment evaluation:

1. Mental status examination
2. Obtain vital signs, weight, waist circumference, and determine BMI.

3. Obtain YMRS, MADRS, CGI-BP-Severity and -Improvement Scales, and C-SSRS since last visit version.
4. Perform physical examination.
5. Obtain laboratories (complete metabolic profile, CBC with diff + platelets, urinalysis, fasting lipids and glucose, and HgA1c level).
6. Repeat ECG.
7. Assess and record adverse events
8. Drug interaction form
9. Record concomitant medication use.
10. Assess study drug accountability.

Final (Follow-Up) Visit Evaluation (Visit 17):

The follow-up period begins upon completion of Visit 16 or ET visit and concludes with a follow-up visit (Visit 17) which occurs 7 days thereafter. Follow-up includes assessment of psychiatric symptoms, adverse events, potential drug interactions, and termination record.

1. Mental status examination
2. YMRS, MADRS, CGI-BP-Severity and –Improvement, and C-SSRS since last visit version
3. Vital signs and weight
4. Urine pregnancy test
5. Assess and record adverse events
6. Potential drug interaction form
7. Termination record

Assessments for Efficacy

The primary efficacy measure will be the percent change in body weight from Baseline to Week 40/Early Termination. Weight will be measured in kg and obtained on the same scale, zeroed at each use, and with the subject in light clothing and no shoes. Secondary efficacy variables will be proportion of patients who have ≥ 5% reduction in body weight, and changes in body weight (kg), BMI, waist circumference, and measures of metabolic variables (fasting lipids and glucose, and HgA_{1C}).

Assessments for Safety

The investigator will conduct and record a medical history at the Screening Visit, including a medication history and all clinically relevant information in conjunction with a Physical Examination. Any abnormalities in the review of systems and exam will be noted in the source documents.

The following assessments will be used to assess safety at each visit: vital signs, taken after the participant is rested and seated for 5 minutes, mental status examination, YMRS, MADRS, CGI-BP-Severity and -Improvement Scales, C-SSRS, urine pregnancy test, concomitant medication form, adverse events, drug interaction form, and study drug accountability. All adverse events will be evaluated as potential drug interactions for those medications used to treat BP (mood stabilizers, antipsychotics, antidepressants, anxiolytics, and sedative-hypnotics) with the drug interaction form. A drug interaction is defined as an AE that is possibly due to an interaction between study drug and a BP medication a subject is receiving.

The YMRS (56) is a widely used, validated, and reliable clinician-administrated instrument that assesses the severity of the symptoms of mania. It consists of 11 items rated on a scale of 0 to 4 (items 1-4, 7, 10, and 11) or 0 to 8 (items 5, 6, 8, and 9) (total score range 0 to 60), with 0 being the absence of symptoms and higher scores representing greater severity of manic symptoms. The total thus ranges from 0 (no symptoms) to 60 (extremely severe symptoms). A mild level of symptoms corresponds to a score of ≤ 12.

The MADRS (57) is a widely used, validated, and reliable clinician-administered measure of depressive symptoms. It consists of 10 items, with each item yielding a score of 0 to 6 (total score range 0 to 60). Higher scores indicate more severe depressive symptoms. Usual cutoff points are: normal is 0 to 6; mild depression is 7 to 19, moderate depression is 20 to 34; and >34 is severe depression.

The Clinical Global Severity item of the CGI-BP (CGI-BP-S) consists of seven ordered categories that describe the global severity of the patient's BP (58). The categories (and the integer values assigned to them) for the purpose of analyses are: normal, not at all ill (1), borderline mentally ill (2), mildly ill (3), moderately ill (4), markedly ill (5), severely ill (6), and among the most extremely ill (7). The Clinical Global Improvement item of the CGI-BP (CGI-BP-I)consists of seven, ordered categories that describe the patient's global condition compared with baseline (58). The categories (and the integer values assigned to them for the purpose of analyses) are as follows: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), and very much worse (7).

The C-SSRS is a summary measure of suicidality, assessing both suicidal behavior and ideation, and has been used at the National Institute of Mental Health and in multi-site industry trials nationally and internationally in a range of therapeutic areas and indications (59).

Regarding adverse event evaluation, participants will be asked if they have experienced any unusual or unwanted symptoms at each visit (none will be suggested, and adverse experiences will be classified and grouped by body system, using a coding system based on the National Adverse Drug Reaction Directory [COSTART]). Adverse events will be recorded on the adverse event form. All adverse events will be evaluated as potential drug interactions with those medications the subject is receiving for treatment of his or her BP (mood stabilizers, antipsychotics, antidepressants, anxiolytics, and sedative-hypnotics) with the drug interaction form. Potential drug interactions will be recorded on the drug interaction form. Other safety evaluations, all done at Screening and Visits 16/ET, will be: physical examination; routine laboratory evaluations, including hematology, serum chemistry, and urinalysis; and an ECG. The interpretation of ECG results will follow the categories "normal", "abnormal", "not clinically significant" or "abnormal, clinically significant" and only "normal" and "abnormal, not clinically significant" results will be allowed at Baseline. Urine pregnancy tests will be performed at every visit post Baseline. Abnormal clinical laboratory or physical exam results will be clinically evaluated to determine if intervention is warranted.

Other Assessments:

The TFEQ is a reliable and validated self-report measure of three domains of eating behavior often deranged in people with obesity: hunger, disinhibition over eating, and cognitive restraint over eating (54). The BES is a valid and reliable self-report scale that assesses the presence and severity of binge eating symptoms (55).

Subject Compliance

Subjects are instructed to bring their unused study medication and packaging to every visit. Subject compliance and drug accountability will be assessed by the investigator at every treatment phase visit by individual pens inspection and entered on the drug accountability log. Compliance will be assessed at each visit with inspection of returned multi-dose pens. Subjects taking 80-100% of prescribed study medication will be considered compliant.

STATISTICAL CONSIDERATIONS:

Sample Size Calculation

The power analysis for this study uses a two-sample t-test on the mean weight change from baseline to week 40 (or endpoint for patients who discontinue prematurely) in the two treatment groups in the modified intent-to-treatment (ITT) sample. This sample will consist of all study participants who: 1) were randomized, 2) received at least one study medication dosage, and 3) had at least one post-baseline efficacy assessment. We expect a 5% attrition rate from baseline to week 1. We therefore expect the proposed sample size of 60 to give an ITT sample of 56. Using this ITT sample size, along with a significance level of 0.05 and power of 0.80, we will be able to detect effect sizes as small as 0.76.

This effect size corresponds to a 4.5 kg greater weight reduction in the liraglutide group vs. the placebo group. The 4.5 kg reduction was calculated (0.76 x 6.0) using an expected standard deviation (SD) of 6.0 kg based on Wadden et al. (SD=7.0 at 56 weeks) and Astrup et al. (SD=5.6 for power analysis). This is a clinically meaningful difference, especially in this population, where many patients are taking antipsychotics, which are associated with weight gain. We expect our primary analysis (longitudinal mixed model) to have more power due to the repeated visit data for each subject (60 subjects x 16 treatment period visits = 960 maximum number of observations).

Statistical Methods

Chi-square, Fisher's Exact, Wilcoxon rank sum or two-sample t-tests will be used to examine statistical differences between the placebo and drug condition on baseline characteristics and categorical outcome measures. The primary analyses will be longitudinal data analyses (LDA) using PROC MIXED (SAS, Cary N.C. U.S.A.). LDA will model the mean change in the primary and secondary outcome measures, over the treatment period, between the placebo and drug condition. LDA is advantageous because it accounts for change over time, includes all data points, and adjusts for the correlation resulting from repeated measures. These LDA models will include variables for treatment, time, and treatment x time interaction. The statistical test for the interaction term will be the measure of a treatment effect. The interaction term will test if the slopes of the regression lines for the liraglutide and placebo groups are different. A group difference (Drug [week 40-week 0] – Placebo [week 40-week 0]) will be reported which corresponds to the interaction term. For the primary outcome of percent change in body weight, only post-baseline data will be used in the LDA model and the difference between treatments at week 40 will be reported. These mixed models will allow for random coefficients (intercept and time variable), as well as an appropriate correlation structure for the error terms to account for within-subject correlation. The best model will be chosen using the Akaike Information Criterion-corrected (AICc). The distribution of the outcome measures will be checked for normality, and transformations will be used when necessary. Also, a transformation on the time variable will be considered to optimize the assumed linear relationship.

Additionally, secondary endpoint analyses will be performed on all outcome measures. Using the last observation carried forward (LOCF), baseline to endpoint change scores will be computed for each measure and two-sample t-tests or Wilcoxon rank sum tests will be used to compare these changes between the treatment groups.

Randomization will be conducted by Genie Groff, the program manager for the Lindner Center of HOPE Research Institute using the program: http://www.randomization.com. Block randomization (with block size of six subjects) will be used to insure relatively equal patients in both the drug and placebo groups. Antipsychotic medications used to treat BP are associated with weight gain and development of obesity (much more so than mood stabilizers). Randomization of subjects will therefore include current antipsychotic use (receiving at least one of the following: asenapine, aripiprazole, cariprazine, chlorpromazine, clozapine, haloperidol, loxapine, olanzapine, paliperidone, perphenazine, quetiapine, resperidone, thiothixene, trifluoperazine, or ziprasidone) as a stratifying factor. Of note, the average number of medications BP patients receive is three. We expect that nearly all patients will be receiving a mood stabilizer and that about 50%-66% of patients will also be receiving an antipsychotic drug. Intermittent missing visits will be treated as missing at random and no special adjustment will be used. The safety population will include all randomized participants with at least one post-baseline safety assessment. Statistical analyses will be conducted by Thomas Blom, MS. All analyses will be conducted using SAS version 9.4 (Cary, N.C., U.S.A.). Hypotheses testing will be two-sided with a significance level of $p \leq 0.05$.

The randomization should balance all demographic and clinical characteristic variables between the two treatment groups and generally no covariates will be used in the analyses. However, if a significant baseline difference exists between treatment groups on a demographic or clinical characteristic variable, this variable will be checked for significant correlations with the outcomes of interest. If a correlation exists, then the variable will be added as a covariate to the efficacy analysis.

DATA HANDLING AND RECORD KEEPING:

All data will be compiled using case report forms (CRFs) that will be specifically designed for this study. Trained research coordinators will complete the CRFs. Data from CRFs will be entered and stored in electronic and secured databases at the LCOH.

ETHICS:

The University of Cincinnati (UC) IRB must approve all protocols, informed consent forms, and study procedures prior to opening the study for enrollment. The investigators will comply with all applicable regulatory and legal requirements, ICH GCP guidelines, and the Declaration of Helsinki in obtaining and documenting the informed consent. A completed Informed Consent Document must be obtained from every participant who takes part in a study prior to performing any study-related activities, including screening laboratories, vital signs, or questionnaires. When a potential protocol candidate is identified, the investigator or research coordinator will discuss the study in detail with the potential participant. An explanation of the study, its risks and benefits, and what would be required of the participant is discussed. The participant will be given a copy of the informed consent document to read in a quiet environment without distraction. The participant will be encouraged to take the consent form home so he or she may discuss it with family members. All questions and concerns are addressed throughout this process by the consenter and/or PI.

If a person decides to participate, he/she is asked to sign the informed consent document only after all questions and concerns have been addressed and the consenter is satisfied that there is a clear understanding of the trial.

The informed consent document must be signed and dated by the participant or legal representative along with the coordinator or investigator obtaining consent.

The original signed informed consent will be kept in the participant's research chart (i.e., source documents) or in the participant's medical record as required by the research unit.

The participant will be given a copy of the signed informed consent document that has HIPPA language written into the consent.

The study will be conducted in accordance with the Declaration of Helsinki.

The study will be conducted in accordance with the ICH GCP guidelines.

STUDY SCHEDULE:

We anticipate recruiting approximately 4 participants per month. We therefore anticipate that total enrollment will take up to 15 months, and total study duration will be up to 24 months. We expect the first participant to be enrolled in September 2016. Following discontinuation of the last study participant, we will clean and analyze the data and write the manuscript for publication, which will take approximately 3 months.

STUDY DRUGS AND MATERIALS:

Study medication will be dispensed through prefilled dial-a-dose pens containing 18 mg of liraglutide or placebo, and the participant can select doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3 mg. The pen is made to be used with NovoFine® or NovoTwist® disposable needles up to a length of 8 mm.

Packaging and Labelling of Study Medication(s)

Participants will be dispensed a prefilled dial-a-dose pen containing 18 mg of liraglutide or placebo that will be labeled according to Ohio regulations and Annex 13 with the name of the Principal Investigator; drug or placebo; date dispensed; and participant number and initials. The pen will be used until medication is finished depending on the participant's dosing schedule and a new one will be dispensed.

Storage and Drug Accountability of Study Medication(s)

New, unused liraglutide pens will be kept in the LCOH research lab refrigerator at 36°F to 46°F (2°C to 8°C). Pens will not be frozen. Participants will be instructed to keep their pens in use for 30 days at 59ºF to 86ºF (15ºC to 30ºC) or in a refrigerator at 36°F to 46°F (2°C to 8°C). They will also be instructed to not freeze the pens and to protect the pens from light.

The temperature in the laboratory refrigerators is controlled automatically and temperatures are recorded daily. The investigator will ensure the availability of proper storage conditions and record and evaluate the temperature.

No trial medication will be dispensed to any person not enrolled in the study. All unused medication(s) will be stored separately from used trial medication(s). Drug accountability for all trial product(s) on the participant and trial site level will be performed by trained research coordinators and pharmacy staff. For participants, accountability will be performed at every visit; on site level the accountability will be performed every 3 months. Return of used/unused trial product(s) and destruction of returned trial product will be performed following Sponsor and Site SOPs.

Auxiliary Supply

No special equipment or other ancillary supplies are expected to be needed for this trial.

Randomization and Blinding

This is double-blind, placebo controlled trial. Pens containing active study medication and those containing placebo will be identical in appearance. The randomization list will be generated by Ms. Genie Groff, the program manager for the Lindner Center of HOPE Research Institute, using http://www.randomization.com. Block randomization method will be used (in blocks of six subjects) to ensure a balanced number of subjects get active drug and placebo, and to prevent long sequences of one treatment assignment. Treatment allocation will be known by one unblinded member of the research staff (Ms. Genie Groff, who generated the randomization list) and kept at a secure location (a locked cabinet in the LCOH Research Institute).

Breaking of Blinded Codes

The code for a particular participant may be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the participant or if demanded by the participant. Whenever a code is broken, the person breaking the code (Ms. Genie Groff) will record the time, date and reason as well as his/her initials in the source documents. If a blind must be broken on an emergent basis, Ms Groff will be contacted. Her work number is 513-536-0715. Of note, Ms. Groff is available 24hours/day, 7 days a week by cell phone (513-276-8388).

The Sponsor will be notified immediately if the code needs to be broken.

All codes (whether broken or not) must be kept throughout the trial period. Accountability of all broken or unbroken codes (hard copy and electronic) will be performed at or after trial closure.

CONCOMITANT ILLNESSES AND MEDICATIONS:

Definitions:

Concomitant illness: any illness that is present at the start of the trial *(i.e. at the first visit).*
Concomitant medication: any medication other than the trial product(s) that is taken during the trial, including the screening and run-in periods.

Details of all concomitant illnesses and medication will be recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication will be recorded at each visit. The information collected for each concomitant medication will include start date, stop date or continuing, dosage, and indication.

For each concomitant illness, date of onset, date of resolution or continuing, and relationship to investigational medication will be recorded.

RISKS AND DISCOMFORTS ASSOCIATED WITH LIRAGLUTIDE (Saxenda®):

Liraglutide 3.0 mg sc injection is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia Syndrome type 2. Liraglutide 3.0 mg sc injection is also contraindicated in patients with a prior serious hypersensitivity reaction to Victoza or to any of the product's components and in women who are pregnant. Common non-serious side effects of liraglutide 3.0 mg sc injection include nausea, diarrhea, constipation, vomiting, headache, decreased appetite, upset stomach, tiredness, dizziness, stomach pain, and changes in lipase levels in the blood.

Possible serious adverse reactions of liraglutide 3.0 mg sc injection include:

Risk of Thyroid C-Cell Tumors
Acute Pancreatitis
Acute Gallbladder Disease
Risk for Hypoglycemia with Concomitant Use of Anti-Diabetic Therapy
Heart Rate Increase
Renal Impairment
Hypersensitivity Reactions
Suicidal Behavior and Ideation

Liraglutide 3.0 mg sc injection is Pregnancy Category X. Therefore, pregnant or lactating women, or women not using adequate birth control, will not be allowed in the study.

Investigators will be available 24 hours/7 days/week for emergencies for study participants. Additional visits to monitor emerging symptoms will be scheduled as needed. The use of all medications will be recorded throughout the study.

Adverse Event Reporting and Definitions:

Definitions

Adverse Event (AE):

An AE is any undesirable medical event occurring to a participant 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 participant has signed the informed consent and until post treatment follow-up period as defined in the protocol. The following should not be recorded as AEs, but recorded as medical history/concomitant illness on the CRF at screening:

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

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 degree of 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 at any dose that results in any of the following:

- Death
- A life-threatening* experience
- In-patient hospitalisation or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Suspicion of transmission of infectious agents

*The term life-threatening in the definition of SAE refers to an event in which the participant 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.

The following adverse events must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable: 1) suspicion of transmission of infectious agents via the trial product; and 2) risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal.

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.

Medication Errors:

A medication error concerning trial products is defined as: administration of wrong drug or use of wrong device; wrong route of administration, such as intramuscular instead of subcutaneous; administration of an overdose with the intention to cause harm, misuse, or abuse of trial product; or accidental administration of a lower or higher dose than intended. However, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

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 participant's daily activities
- Moderate: Marked symptoms, moderate interference with the participant's daily activities
- Severe: Considerable interference with the participant'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 participant signed the informed consent
- Recovering: The condition is improving and the participant is expected to recover from the event. This term should only be used when the participant has completed the trial
- Recovered with sequelae: As a result of the AE, the participant 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: This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved." An AE with fatal outcome must be reported as an SAE.
- Unknown

The sites will collect the following information at minimum for each SAE and provide it to the University of Cincinnati IRB and Novo Nordisk within 72 hours:

1. Study name
2. Patient identification (e.g. initials, sex, age)
3. Event (preferably a diagnosis)
4. Drug
5. Reporter identification (e.g. Name, or initials)
6) Causality
7) Outcome

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 participant has signed the informed consent and until the end of the post-treatment follow-up period as stated in the protocol. The site intends to comply with all local legal, regulatory, and IRB requirements related to AE reporting. The site and the principal investigator will be responsible for reporting of adverse events including SAEs, suspected unexpected serious adverse reactions (SUSARs), and SADRs, to the competent authority and University of Cincinnati Institutional Review Board based upon federal regulations and local IRB policies. All SAEs will be reported to the IRB and Novo Nordisk within 72 hours. In addition, the site and principal investigator will report to Novo Nordisk all SADRs or any other event reported to regulatory authorities. The events shall be sent to Novo Nordisk at time of submission to health authorities or within 15 days from the site becoming aware of such adverse events, whichever comes first." **Follow-up of Adverse Events**

During and following a participant's participation in a clinical trial, the investigator will carefully assess and provide adequate medical care to the study participant for any study-related adverse events, including clinically significant laboratory values related to the study. The Lindner Center of HOPE will decide on a

case by case basis whether to reimburse the participant for their out of pocket health care expenses. This will be determined by the medical director of LCOH who is not a part of the study team. Medical expenses that are deemed clearly related to study participation will be reimbursed. (This language will be included in the consent form.)

All adverse events classified as serious or severe or possibly/probably related to the trial product will be followed until the participant 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 will 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

All female study participants will be instructed to notify the site and the investigator immediately if they become pregnant. The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age. The investigator must report to Novo Nordisk about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant. Reporting of pregnancy by the investigator will occur within the same timelines described above for reporting of Adverse Events. Pregnancy complications will be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this will be reported and followed up as a serious adverse event.

Precautions/Over-dosage

Effects of overdose when treated with liraglutide might include severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment will be initiated according to the participant's clinical signs and symptoms. All participants in the trail will be appropriately educated on how to use the pen in order to avoid overdosing and how to proceed in event of accidental overdosing

LIABILITY AND PARTICIPANT INSURANCE:

In the event that a participant becomes ill or injured from participating in this research study, emergency medical care will be provided to them. The Lindner Center of HOPE and University of Cincinnati College of Medicine will decide on a case by case basis whether to reimburse the participant for their out of pocket health care expenses.

The principal investigator will be responsible for the conduct of the study and Lindner Center of HOPE 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) 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.

PUBLICATION PLAN:

We will submit abstracts of the study results to psychiatric and obesity scientific meetings such as the American Psychiatric Association Annual Meeting, Obesity Week, and the Society of Biological Psychiatry. We will also submit a manuscript of the study for publication to a leading obesity or psychiatric journal, such as Obesity, the American Journal of Psychiatry, or the Journal of Clinical Psychiatry. We will register the study with a publicly assessable database such as clinicaltrials.gov.

Fasting Blood Script for Phone Screens:

During the screening visit we will obtain a fasting blood sample. Fasting blood tests require you to stop eating and drinking anything (with the exception of plain water) at least 8 hours before you visit. Please drink as much water as you like, but no other food or drink. Black coffee or black tea - without any sweetener or creamer - is acceptable. After the blood draw we will provide a snack and drink. If you have a medical condition that prevents you from fasting 8 hours, please let us know before the visit and we will make other arrangements. Please let us know if you have any questions about the fasting procedures.

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Table 1: Schedule of Assessments

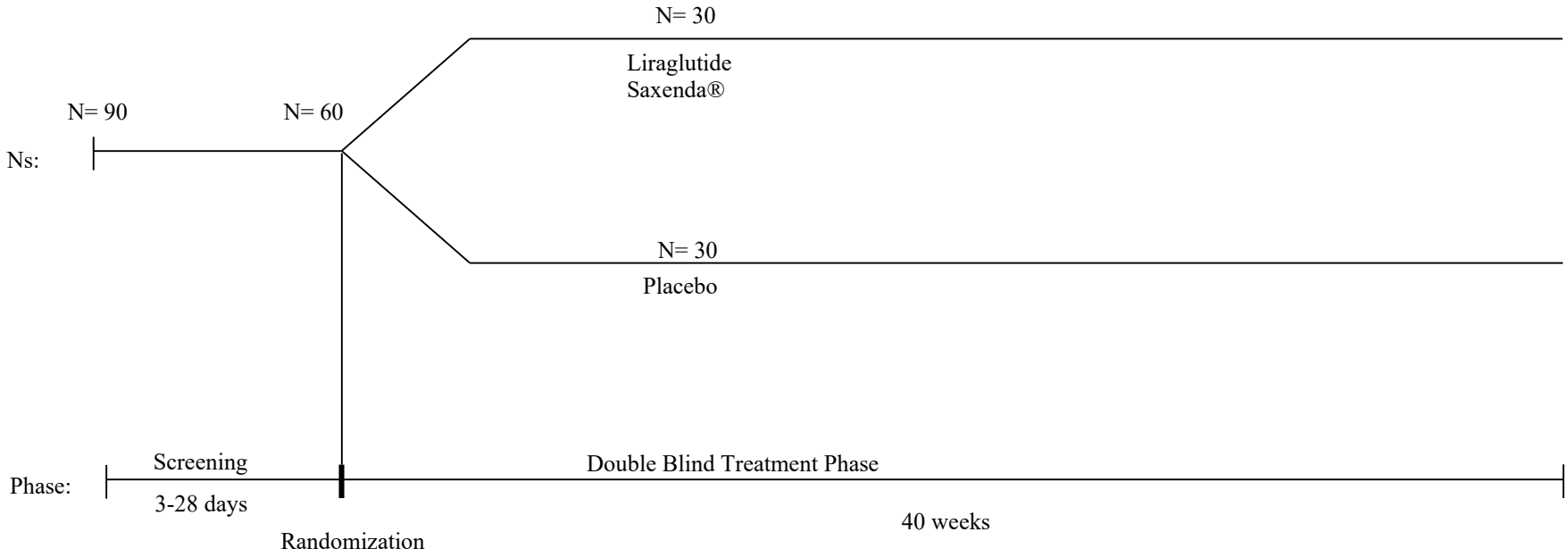
Visit	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ET**	**17**
	(Screening)	**(Baseline)**																	**(Follow-up)**
Assessment Week	**up to -4**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**41**
Assessment Day	**-3 to -28**	**0**	**7**	**14**	**21**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**140**	**168**	**196**	**224**	**252**	**280/ET**	**287/Any**
Informed consent	**x**																		
Psychiatric evaluation	**x**																		
Medical history	**x**																		
SCID	**x**																		
Mental Status Examination	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Inclusion/exclusion criteria	**x**	**x**																	
Physical examination	**x**											**x**						**x**	
Demographics	**x**																		
Vital signs	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Height[a]	**x**																		
Weight[a]	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Waist circumference		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Clinical laboratory tests[b]	**x**							**x**				**x**						**x**	
12-lead ECG	**x**							**x**				**x**						**x**	
Serum pregnancy test	**x**																		
Urine Pregnancy test		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Urine drug screen	**x**																		
YMRS	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
MADRS	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
CGI-BP-S	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

CGI-BP-I			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lifestyle counseling		x				x		x		x		x	x	x	x	x	x		
TFEQ		x				x		x		x		x	x	x	x	x	x	x	
BES		x				x		x		x		x	x	x	x	x	x	x	
C-SSRS- Baseline Version	x																		
C-SSRS- Since Last Visit Version		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Suitability to remain in study	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Investigational product dispensed		x	x	x	x	x	x	x	x	x	x	x	x		x	x			
Investigational product returned			x	x	x	x	x	x	x	x	x	x	x		x	x		x	
Compliance assessed			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug interaction form	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Termination record																			x

[a]Weight (using a calibrated scale) and height to be measured without shoes.

[b]Laboratory samples will be obtained when the subject is fasting and will include CBC with diff, Metabolic profile, lipids, HgA_{1c}. Participants must fast for 12 hours prior to laboratory samples being collected.

Figure 1: Study Schematic



Potential Drug Interaction

Subject #: _____ Date:_____

1. Was there any information suggesting the subject had an interaction between liraglutide and a psychiatric mediation?

   ☐ Yes ☐ No

   If YES, provide a complete description of the putative interaction.

   _____

   _____

   _____

2. Please list all psychiatric medications involved in this interaction.

   _____

   _____

   _____

3. Was any action taken to manage the interaction?

   ☐ Yes ☐ No

   If YES, please explain:

   _____

   _____

   _____

4. Outcome of interaction:

   _____

   _____

   _____

   _____